THE PHYSIOLOGY OF THE CONTINUITY OF LIFE



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THE PHYSIOLOGY
OF THE
CONTINUITY OF LIFE

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MACMILLAN AND CO, LIMITED

ST. MARTIN'S STREET, LONDON

1926

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FOREWORD

PHYSIOLOGY may be defined as the study of the adaptations of living things to their environment The greater part of every physiological course is taken up with the consideration of these adaptations in the individual, of how it is acted upon and reacts upon its surroundings and of how its various parts interact on one another

But of equal interest is the consideration of how these adaptations arise and of how they are propagated from one generation to another These questions are generally considered in courses of biology, where there is a tendency to deal with them from a morphological or structural standpoint. But they are really physiological problems, since fundamentally they depend upon the chemical changes, the metabolic processes, which are the essential characteristics of life.

In the study of every branch of physiology there is a tendency to give and to accept *ex cathedra* teaching, which is soul destroying alike for a teacher and the student Progress is made possible only by refusal to accept such teaching and by the

insistence on the presentation and consideration of the evidence for and against every statement. Authoritative text-books have played a great part in obstructing the advance of science Helmholtz is credited with saying that his advances were made by re-investigating the statements found in such books

Perhaps in no part of physiology is the tendency to authoritative teaching more seen than in that which concerns reproduction and inheritance Certain conclusions have been generally accepted as *choses jugés*, about which further discussion is deemed unnecessary, but, upon examination, many of them are found to be mere hypothesis The dictum that life can only arise from life, the so-called Mendelian laws of inheritance, the part played by chromatin in inheritance and in the determination of sex and the impossibility of the transmission of acquired characters may be cited as examples

In approaching the study of the Continuity of Life I have tried to keep an open mind and to present evidence and not dogma, and I do not hesitate to ask my readers to make the necessary intellectual effort for judging the value of the evidence Our motto must be "*Jurare in verbis nullius magistri*"

With these considerations in view, I have put together this book which is based upon Lectures delivered to the students of Physiology in the

University of Glasgow during the past five years, during which time the course has gradually evolved into its present form Those who attended had already some knowledge of Chemistry, Zoology, Human Anatomy and General Physiology, and they therefore had some training in the evaluation of evidence Those parts of the subject which seem to me to require discussion have been dealt with at greater length than others of equal importance

No attempt has been made to cite all the original papers which have been considered, but references are given to some which have not yet been absorbed into the standard books, and lists are given of books which the student may consult.

The figures are reproductions of lantern slides with which the lectures were illustrated I have to thank Prof Morgan and Messrs Lippincott Co , Messrs Methuen & Co., Messrs Jonathan Cape, the Cambridge University Press, Dr Quinby and Messrs D Appleton & Co , Professors K Pearson, Teacher and Agar for permission to reproduce several of these It gives me pleasure to thank Mrs Cathcart for reading proofs—and Miss Agnew for assistance in preparing the indices

D N P

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CHAPTER I

LIFE AND HEREDITY

1 THE ESSENTIAL CHARACTERS OF LIFE

In approaching the consideration of the continuity of life the question at once arises, "What do we mean by life—what are its essential characters?", and in trying to answer this it must be recognised that any definition must be applicable not only to the highest but also to the lowest forms, to plants as well as to animals

Manifest movements, apart from growth and reproduction, are not essential properties of living things, nor is there any evidence that consciousness is generally associated with them

The consideration of the question of what life is may best be approached by inquiring if there is any kind of substance or substances which, under suitable conditions, can manifest all the marvellously diverse phenomena of life in structure and in action

The characters which seem common to all living things and the possession of which endows them with all the potentialities of life are

1st The power under suitable conditions of using the energy derived directly or indirectly from the sun to build themselves up by assimilation, not by mere accretion, to transmute what they use into their own substance, to make it flesh of their flesh

2nd Their existing in a particulate condition separate from their surroundings so that they can be acted upon by and react upon their environment

1st **The Use of Solar Energy for Construction.** The investigations of the late B Moore and others indicate that certain inorganic materials in a state of very fine subdivision, which is known as the colloid state, manifest the property of enabling solar energy to bring about the initial stages of the process The observation that, in the presence of colloidal ferrous hydrate, formaldehyde (CH_2O) is produced in sunlight from CO_2 and H_2O seems to show that the difference between living and non-living in the colloidal state is in degree rather than in kind Baly and his co-workers have induced the same change by exposing carbonic acid to ultra-violet rays The formaldehyde so produced is activated by more rapid rays Its molecule may then be represented (H C—OH) with trivalent carbon—and this at once tends to polymerise and to form the six carbon sugars

While it has for long been known that the nitrogen of the atmosphere may form nitrates and nitrites, recently Baly and his co-workers have

demonstrated that formaldehyde under the influence of ultra-violet rays may be made to link to nitrites to form formhydroxamic acid (HO CH NOH) They have further shown that formhydroxamic acid may react with activated formaldehyde to give complex nitrogenous compounds, some of an alkaloidal nature, some having the characters of the amino-acids, the " building stones " of the proteins which are the essential constituents of all living matter

There is thus good evidence for the formation of highly complex organic substances from inorganic matter, under the influence of solar energy, and the process is very similar to that which occurs in the complex colloids of living matter

Whether or no this synthesis goes as far as the production of living matter, of substances having the characters we have postulated, there is of course no doubt of the continued creation of life from inert inorganic matter by the action of solar energy through green plants Life is constantly being produced upon the earth

> " For of old the Sun, our Sire,
> Came wooing the mother of men
> Earth
> And born of their starry nuptial joy
> Are all that drink of her breast "

Harvey's dictum " omne vivum ex ovo " even if read " ex vivo " may or may not be true, and all that Pasteur proved is that such structures as

bacteria do not appear under his experimental conditions except from bacteria Neither disprove the possible origin of living things from inorganic matter

Admitting that living things have the property of building themselves up from simple inorganic matter under the influence of solar energy and of thus growing, the question of the possibility of the continuance of the process in the absence of direct sunlight with its ultra-violet rays has to be considered Under this condition the solar energy stored in living matter by the formation of such complex substances as sugar ($C_6H_{12}O_6$) may be liberated and used by other living matter, thus life lives upon life The tendency of such complex molecules to be oxidised and to break down into simpler molecules is well known, and, in the breaking down the stored energy is liberated. The acceleration of such processes by *catalysts* is familiar to every chemist Living matter under certain conditions manifests this catalytic action by the development of the so-called *enzymes*, and thus more rapidly liberates energy for its own use —primarily for building itself up, secondarily for work and heat production

The process of growth in which solar energy is used indirectly is well exemplified by yeast torulae growing in a solution of glucose ($C_6H_{12}O_6$), ammonium nitrate (NH_4NO_3), disodium phosphate (Na_2HPO_4), and potassium sulphate (K_2SO_4), which

solution contains the essential elements of living matter Kept at a suitable temperature the yeast increases in bulk, the torulae dividing and reproducing The *material* is derived from the elements in the solution, the *energy* is got from the breaking down and partial auto-oxidation of the glucose into alcohol (C_2H_6O), carbon dioxide (CO_2), and water (H_2O)

In man the material required for growth, and the energy necessary for growth, work and heat, are obtained from the materials built up under the influence of solar energy by green plants His fields of wheat are but traps for the sun's rays, and he gets his energy just as much from the sun whether he consumes the bread directly made from the wheat or feeds upon the bodies of animals fed upon plants

In living matter, as in most highly complex chemical substances, disintegrative changes are constantly going on Theoretically, the energy liberated by these should just suffice to build up the same amount of living matter as that disintegrated, and hence, if the solar energy, either directly available or indirectly made available, is forthcoming in addition, energy for growth is provided and the living matter can increase It has been calculated that a single tiny infusorian, *Paramoecium*, multiplying under completely favourable conditions would form a mass of living matter the size of the world in a year

Life, then, implies a constant breaking down and a constant building up A thing is living only in virtue of the constant chemical change As Sir Michael Foster wrote "We may speak of protoplasm as a complex substance, but we must strive to realise that what we mean by that is a complex whirl, an intricate dance, of which what we call chemical composition, histological structure, and gross configuration are, so to speak, the figures"

2nd **Particulate Existence** As to the second character of living things, a substance or mixture of substances, with the properties just considered, if it is to develop the familiar behaviour of living matter in all its diverse forms, must exist in a particulate condition, as units separated from their environment It is impossible to conceive of a mere solution or suspension, even if it possessed the power of using solar energy for its increase, developing all the marvellous diversity of living things But in a particulate condition it can be acted upon by its surroundings and may thus undergo modification

Such individual separate masses are subjected to certain conditions

(1) The supply of the material for growth and of solar energy must come from the surface As a sphere increases in size, the mass increases more rapidly than the surface Hence, with unit of growth, the supply of energy from the surface per

unit of mass will decrease and the chemical changes will be modified

(ii) The differentiation between the unit and its environment is kept up by the surface tension between them, and the potential size of the unit is regulated by its surface tension The surface tension is modified, among other ways, by the chemical nature of the substances in apposition

(iii) Hence any chemical change in the unit may so modify the surface tension as to lead to a change in shape, movement, or to a division into two smaller units, phenomena which are manifested by camphor upon water

(iv) The result of division is reproduction—two smaller masses taking the place of the parent mass Unless the unit as it grows responds in this way it must perish—continuity of life is possible only by division, by reproduction Reproduction is thus the most fundamental adaptation to environment

(v) In each of the daughter masses formed the same chemical changes will go on as went on in the parent mass when of the same size, provided that the environments do not alter in such a way as to modify them Newton's first law—the law of inertia—is applicable to the molecular changes in these units

The course of development in every living thing, following as it does step by step the development of its predecessors and the marvellous uniformity in the members of each species, is impressive

testimony to the truth of this conception of *hereditary inertia* as the basis of heredity

The essential part of the conception of heredity is that it *is simply transmission, not of structure but of modes of molecular motion—that it is kinetic, not static or structural* Structure and form are but the expression of chemical changes A recognition of this is fundamental in all study of reproduction and heredity

The Effects of Environment. Adaptation. Newton's first law not only formulates the conception of inertia but it also indicates that this inertia may be acted upon from without So the hereditary inertia of the molecular movements of living units may be modified by changes in environment, and upon this depends the possibility of the development of living things in all their varieties If changes in environment lead to changes in the chemical processes in the living units they may so alter the conditions that continued existence is impossible, or may lead to adaptation of the chemical changes, provided that the modification is not detrimental to existence under the altered conditions Thus an increase in calcium in the surrounding water might lead either to an accumulation of soluble calcium in the living unit and to a stoppage of the chemical changes, or to a precipitation of calcium in insoluble form without interference with the essential chemical changes, and the deposition might prove

of use in supporting the substance of the unit, and, by the modification extending over several generations, might ultimately lead to the development of a skeleton of some sort, with a modification in form of the original unit

Slight differences in surface tension at various parts of the surface, due to local changes in the composition of the surrounding medium, may lead to different rates of osmosis or diffusion and to differentiation of chemical changes and hence of structure in the various parts of the unit, so that these parts may act in different ways and perform separate functions These differences may be more or less permanent, and each must be linked up and co-ordinated with all the others

In the unicellular *Protozoa* the single cell has to perform the functions of reproduction and of adaptation to environment by which alone continuance of life is possible Complexity of action and of structure in many of these simple organisms has reached a high development



FIG 1 —*Poterodendron* A single individual of a colony, showing cell body with capsule, flagellum and myoid fibre (From Verworn)

In the infusoria an endless variety of physiological and anatomical adaptations to surroundings has developed. In *Poterodendron* the cell has differentiated into a cell body surrounded by a cup-like capsule, a long process or flagellum

and a contractile stalk by which the cell is drawn down when the flagellum is touched, in fact, a receptor and effector arrangement, a neuro-muscular system *Noctiluca* has developed a series of substances and ferments by means of which it gives off light when stimulated *Vampyrella spirogyrae* responds to the special stimulus of the

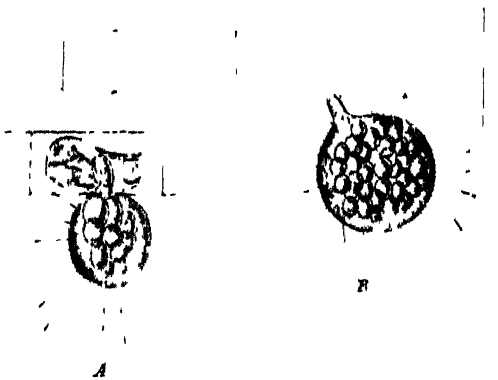


FIG 2.—*Vampyrella spirogyrae* (*A*) Boring into and (*B*) engulfing the contents of a spirogyra cell (From Verworn after Cienkowski)

chemical substances coming from spirogyra filaments by swimming towards them, fixing itself upon them, boring its way into them and consuming their contents (Fig 2)

As an example of the differentiation of the reproductive part from the protecting and nourishing part of such unicellular organisms we may take *Paramoecium* as an example In this infusorian the true reproductive part of the cell is the micro-nucleus which plays a most important part in conjugation (p 62) The somal part of the cell is represented by the large macro-nucleus

with its surrounding protoplasm furnished with a covering of cilia, with a contractile vesicle and other structures (Fig 3)

In *multicellular* organisms these adaptations to changed environment become even more complexly developed In them the zygote or the germ cell throws off, sometimes very early in division, *e g*

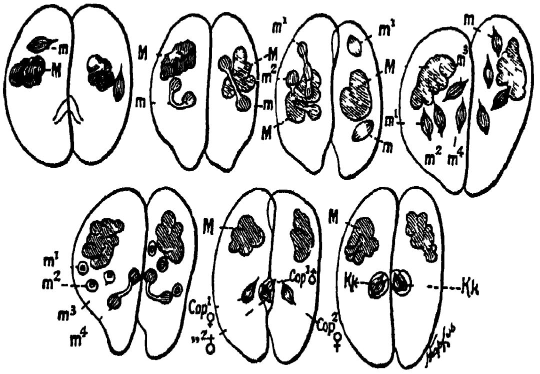


Fig 3 —Paramoecium cells in conjugation In the top left hand figures the micro and macro nuclei are seen in each cell In the other figures the division of the micro nucleus and the transference of one part from cell to cell is shown (From Selenka Goldschmidt)

in *ascaris* from the very first division, precursors of the cell mass which forms the body or soma for the purpose of nourishing and protecting the germs or gametic cells The somal cells perish with each generation, the gametic cells are potentially eternal In each generation, either parthenogenetically or after fertilization, they undergo the same process of division They throw out similar somal cells, which, obeying the laws of inertia, undergo precisely the same changes unless these are modified by action from without, and variations are thus introduced

These somal cells must be adapted to their environment or perish

In the course of adaptation of function and structure there is no question of evolution from a lower to a higher form, the process may be towards simplification just as well as towards complication The parasitic worm, living in its bath of warm, pre-digested food, is just as perfectly adapted as man himself or the swallow speeding through the summer air

If the surrounding conditions are constant and unvarying no great complexity of arrangement is required The intestinal worm needs but a simple arrangement of its somal cells to nourish its reproductive mechanism, but, as the organism is subjected to greater and greater variations of its surroundings, means of adaptation to these must be evolved When the food is no longer circumambient it has to be secured and digested, and sent with the necessary oxygen to the muscular tissues which are developed to enable the animal to escape from adverse conditions or to secure its food The products of combustion have to be got rid of, and the combustion must not be allowed to raise the temperature of the body above that compatible with life Means of detecting the presence of food or of danger are necessary, and these must be linked up to the muscular system to bring about the necessary responses For the proper action of these

muscles the whole body must be kept balanced and supported

It is to effect these purposes that the various "systems" have evolved

Receptive organs, which are acted upon by the surroundings, develop at the surface (1) Organs in the skin acted upon by contact, by changes of temperature, and by injurious influences (2) The accumulation of organs in the anterior part of the body to warn the animal of the conditions it is approaching—the nose, eyes and ears

These receptors are again all linked up with one another in the nervous system, in man chiefly in the basal ganglia of the great brain

Their stimulation leads to movements, more or less appropriate, by reflex action, or with the co-incidence of changes in consciousness—sensations—to the so-called voluntary movements Escape from danger and the acquisition of food are thus secured

The food has to be prepared in the organs of digestion, to be absorbed into the blood, to be pumped throughout the body by the circulation, which must also carry the oxygen taken into the lungs by respiration, since this is required for the liberation of energy from the food by the muscles The blood in the circulation must carry away the waste products, and these must be eliminated by the organs of excretion, the lungs and kidneys

Not only must all these systems be developed, but they must respond adequately and harmoniously They must be physiologically adapted They must adapt themselves to the endless changes in environment to which the body is subjected The development of structure—static development—and kinetic adaptation of the action of each one and all of these structures to every change in environment are equally important

The kinetic adaptation must be sufficiently prompt if health and life are to be maintained A man tries to escape from some danger or to hunt his prey, he starts to run, every muscle is in action liberating energy for its contraction The demand for oxygen by the muscles is at once increased The blood-vessels in the muscles dilate, and those of the non-acting organs, *e g* in the abdomen, contract, to increase the flow of blood to the muscles The action of the heart is increased to keep up the pressure of blood, the breathing is augmented to get an adequate supply of oxygen and to get rid of the carbon dioxide The glycogen of the liver is changed to sugar and sent to the muscles to supply energy Unless each of these changes takes place to an appropriate and proportionate amount collapse must follow An increased flow of blood is useless if the blood is not properly oxygenated A dilatation of the vessels is of no avail unless the heart's action is simultaneously increased As indicated by these

examples the adaptations must be general and co-ordinated All the various organs must act in concert

The fundamental adaptations upon which the maintenance of life depends occur without the necessary implication of consciousness But in others consciousness is involved Periods of intense mental work may alternate with periods of muscular work and with periods of sleep There must be a nice regulation of the oxygen supply to the brain and to the muscles under these varying conditions, involving not merely alterations in the heart and breathing but also in the condition of the peripheral vessels

Social life and civilisation, too, require adaptations and adjustments, often of considerable moment, such as the suppression of emotional responses It may be urged that these are not of the same fundamental nature as those already dealt with, but, since man's development has been the result of his communal life, such adjustments must be considered as physiological They are not necessarily produced by conscious suppression, but they have been developed by the elimination of those in whom the emotional impulses are not adequately checked

The possibility of development of complexity in action and in structure at first sight appears limitless But it may reach a point at which it becomes a source of danger The interdependence of the

various structures and their actions may be so absolute that any small interference with any one may upset the action of the whole system The human body, like our modern civilisation, has become so complex, the parts so interdependent on one another, that it is self-destructive

In man, in whose life consciousness plays so prominent a part, another factor tends to interfere with the continuity of life While the soma was primarily developed to nourish and protect the gametes, and so to secure the continuance of life, its relationship with its environment may become so all absorbing that its primary function may fall into abeyance The life of the species may be sacrificed for that of the individual In considering the decreased fertility of more civilised races this possibility seems worthy of consideration

2 THE TRANSMISSION OF ADAPTATIONS

The question has naturally been raised—" How can adaptation of the body be transmitted to the offspring which are formed from the germ cells and not from the body cells which have become adapted? "

Manifestly adaptation may take place in two different ways

Since in all living things there is a certain range of variation to one or other side of a mean, some individuals may be better adapted to certain

changes in environment than are others, and hence they will survive and reproduce

The development of the individual is an expression of the changes in the germ cell from which it arose, and hence differences in individuals must

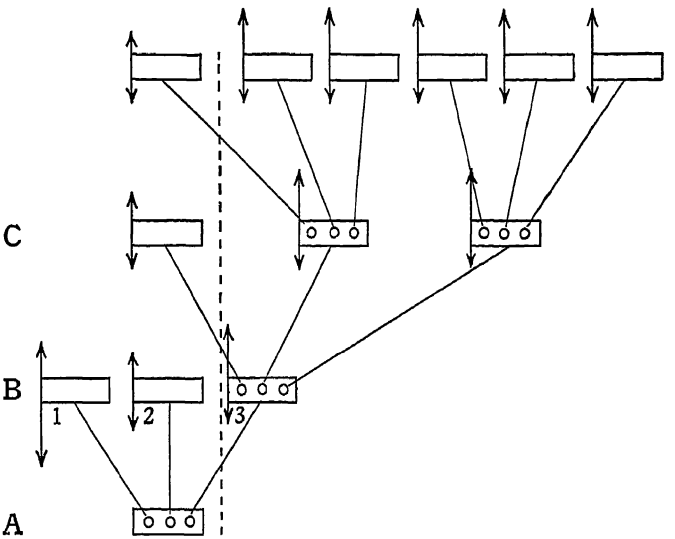


FIG 4.—Diagram of the survival of the offspring best adapted to the environmental conditions [——] represents individuals, O the germ cells The deviation of metabolism from the mean is represented by the direction and length of the arrows The increase of individuals with metabolism suited to environment is shown on the right

be correlated with differences in the germ cells which will tend to breed true The offspring of the better adapted individuals will thus tend to resemble them

Darwin's great work undoubtedly was the demonstration of the possibility of development of new forms by artificial selection and the application of this fact to explain natural selection

Von Vries and others have maintained that changes in form have arisen by more violent and

marked alteration in the germ cells, so marked that the new individual is at once apparently different from the common stock Such "mutants" tend to breed true, and hence new species may originate.

There must of course be some explanation of these so-called accidental occurrences The germ cell must have been modified through changes in the external conditions acting either directly or through the body They are most apt to occur in plants and animals kept under artificial conditions

But, while recognising that adaptation may be secured by the preservation of the more suitable variants, and that it may even occur through the appearance of mutants widely different from their parent stock, there is also evidence that modifications of the body, functional or structural, may so modify the germ cells that their line of development is altered

It must be recognised that this means a modification in the course of hereditary inertia, that it is of the nature of the "force acting from without" and that its action must be fundamental if it is to be effective

Over the possibility that acquired characters can be transmitted one of the great biological battles has raged

Lamarck and even Darwin accepted it, but the post-Darwinians headed by Weismann have strongly opposed it

In my young days the dicta of Weismann were generally accepted by many of us without any study of the original evidence We were too ready —"*Jurare in verbis magistri*" We were credulous.

But the evidence, not only as presented by Weismann and his followers, but as afforded by other observers has to be faced and evaluated

Biological investigation has shown that a large number of acquired modifications are not capable of transmission, but there is also evidence that, if the somal change is of such a character that the germ cells are affected, it can be propagated

This raises the question of how far the somal cells are distinct from the germ cells and how far they can act upon them Evidence will be adduced later to show that they are not independent and that they do act, *e g* in parthenogenic reproduction and in sex determination (p 101 *et seq*)

A very striking illustration of what appears to be an action of somal cells upon the gametes is described by Morgan in the parthenogenetic reproduction of plant-lice, *aphids*, in which the complication of the influences of the male is excluded From the wingless lice winged insects may appear totally different in appearance and character from their parents These in the next generation may produce wingless insects That the change in the development of the germ cell may be determined through the soma has been shown by Shinji on the rose aphid (quoted by

Morgan) He placed twigs of the rose in sand moistened with water containing different reagents and got marked variation in the production of wingless and winged individuals Thus in $NiSO_4$ there were 955 winged to 5 wingless, while in sodium salts there were 2 winged to 1029 wingless Other substances gave similar, often smaller, variations in the proportions

Another instance of this modification of the germ cells by nutrition is afforded by the investigation of Shule and Ladoff and of Whitney on Rotiers [1] They showed that the proportion of male producing eggs by the parthenogenic females may be increased according to the former investigators by increasing the supply of oxygen according to the latter by increasing the supply of green flagellates as food

Fischer records the production of a darker colour in certain moths by exposing the larvae to low temperature, and states that the colour was transmitted to the next generation even when the animals were kept under normal conditions

Tower studied the effect of dry heat on the potato-beetle *Leptinotarsa decemlineata* He found that when applied to the caterpillar stage some changes in marking were produced, but no change was observed in the beetles which emerged from the chrysalis If heat were applied to the chrysalis, the beetles were dwarfed and bleached, but their

[1] *J Exp Zool* 1917, 18, 24, 101

young were normal When heat was applied to the mature insect no manifest change was observed, but the offspring were dwarfed and bleached and their offspring showed the same characters Further, these modified beetles, when bred with the normal, gave progeny which followed the Mendelian "Law," the normal being dominant to the modified

Even Weismann was prepared to admit that the germ cells may be modified to such an extent by alterations in the environment of the body that modification in the body structure of the next generation may be produced. But he maintained that this action is direct upon the germ cells and he called it "parallel induction"

Such a theory might explain the changes produced in unicellular organisms and in invertebrates, but it is difficult to see how it can be applied to vertebrates in which the germ cells are situated deeply in the body and are nourished by the somal blood, and where, at least in mammals, the temperature is controlled by the heat regulating mechanism of the body

Many cases of change of character in vertebrates associated with changes in external conditions are on record

Kammerer[1] has amassed considerable evidence from which one or two examples may be described

[1] In his book, *Inheritance of Acquired Characteristics*, 1924, Boni & Liveright, New York, Kammerer is a somewhat unsatisfactory advocate of his views

The midwife toad *Alytes obstetricans* copulates on land, and the male does not develop the clasping pads on the hands which are characteristic of toads which copulate in water The female lays comparatively few eggs, about 60 in place of the 700 or more produced by the ordinary toad, and these eggs are larger and have more yolk than the eggs of the ordinary species When they have been fertilized by the male, he winds a string of eggs round each hind leg, and they remain there till hatched The male toad visits ponds and the larvae are hatched out in water When hatched they are further developed than the larvae of other toads and the gill-case has already grown over the gills

By keeping the toads in warm dry surroundings, Kammerer forced them to spend more and more time in water till at length they mated there The eggs fell to the bottom and only a few developed After repeated spawning in water the females yielded more and smaller eggs and the tadpoles hatched earlier and had a longer external gill

When the female had been long accustomed to hot dry conditions, and had acquired the habit of spawning in water, the tadpoles when hatched had three external gills, and when they developed to sexual maturity they spontaneously went to water to spawn

In the next generation males were produced with clasping pads Kammerer has carried his

which has a well-marked temperature regulating power The change in these germ cells must have been secondary to changes in the body

Not only is there evidence that modifications which may be supposed to be of advantage may be transmitted, but changes manifestly prejudicial may also lead to such changes in the germ cells that they are propagated

Guyer and Smith find that when the pulped crystalline lens of rabbits is injected into fowls, so as to produce a cytolytic serum, the injection into rabbits of this serum is followed by some of the young having eye defects These may be transmitted to succeeding generations not only by the females but also by the males

Bagg[1] has recorded the inheritance of deformities and deficiencies produced on male and female mice by means of X-rays In 16 per cent one kidney was absent In matings of males and females with only one kidney, both kidneys were absent in two of the young If such gross and prejudicial changes in the soma may modify the development of succeeding generations, it seems equally probable that advantageous changes may operate in the same way

The inheritance of the epileptic condition induced in guinea pigs by section of the sciatic nerve, which was described by Brown Sequard, is of the same nature His observations have been re-

[1] *Proc Soc Exp Biol Med* 1924, 21, 146 and 238

peated, but they require re-investigation on a large scale

The investigations of Tornier seem to show that unhygienic conditions account for the development of abnormalities in the form of goldfish bred in China, *e g* distorted tails, elongated fins, etc He states that when these abnormal fish are allowed to breed under healthy conditions only about 10 per cent of the offspring show the abnormal characteristics, but if allowed to breed with decreased supply of oxygen as many as 90 per cent may show abnormalities He considers that this is due to what he called "germ weakness" It is immaterial whether Tornier's explanation of the effect of germ weakness being a loss of control of the water content of the developing zygote is correct, the fact remains that, in conditions where germ weakness may be expected to occur, mutants tend to develop, and MacBride very justly points out that these variations from the standard occur in plants in cultivation and in animals in confinement, when germ weakness might be expected to exist

It is difficult to understand how the development of instinctive actions, which are really inherited conditioned reflexes, can be explained unless on the view that modifications in the action of the soma may be transmitted It might of course be argued that there is a natural selection of animals with instincts suited to the environment,

and that those which do not develop the reaction die out

Pawlow in 1922 recorded certain interesting experiments upon mice which seem to oppose the latter explanation He found that the conditioned reflex of response to a bell in inducing feeding required 300 repetitions in the first generation of mice, but in the second generation only 100, and in the third 50, and in the fourth only 5

An excellent discussion of the question "Are acquired characters inherited?" is given by W E Castles in Chap IX of his *Genetics and Eugenics* He concludes

"If the germ-cells are capable either directly or indirectly of modification by outside agencies, evolution guided by the environment must be in some measure at least a reality The truth then lies neither in the extreme Lamarckian view that all acquired characters are inherited nor in the extreme Weismannian view, that no extraneous influences modify the germ-plasm, but somewhere in between"

The view of the Weismannian Eugenist is—Determine the type you are to breed to, and select for breeding those members of the community who approach it Education or the cultivation of the characters in the individual are futile for the race

The Eugenist who considers that the evidence we possess shows that acquired modifications of

the body may modify the gametes, and so the coming generation, is able to believe in the beneficial effects of education, using the term in its broadest sense, upon future generations

3 THE MENDELIAN THEORIES OF INHERITANCE

The study of heredity, or, to use a wider term, of genetics, was enormously stimulated by the re-

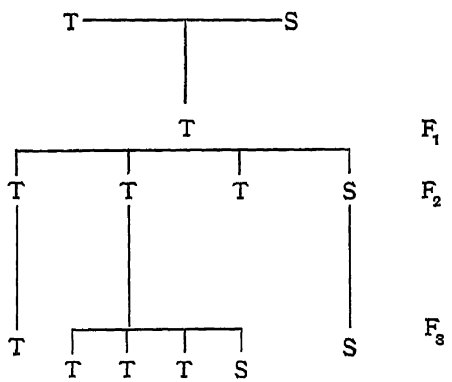


FIG 5 —Scheme of Mendelian inheritance through three generations

discovery, in 1890, of the old observations and conclusions of Mendel

In 1865 the Abbé Mendel recorded the results of a long series of experiments upon heredity in peas He first found that when a tall form is crossed with a dwarf form the first generation F_1 are all tall, but that in the second generation the proportion of tall to short is as 3 to 1

In the third generation, F_2, if the dwarfs are self-fertilised they produce dwarfs only when the tall forms are self-fertilized they produce tall and short in the proportion of 3 to 1, but sometimes tall only

Other characters were found to behave in the same way (Fig 5)

The evidence which he collected seemed to Mendel to indicate that the results might be explained by assuming that various characters occur in pairs, one opposed to the other, allelomorphs as

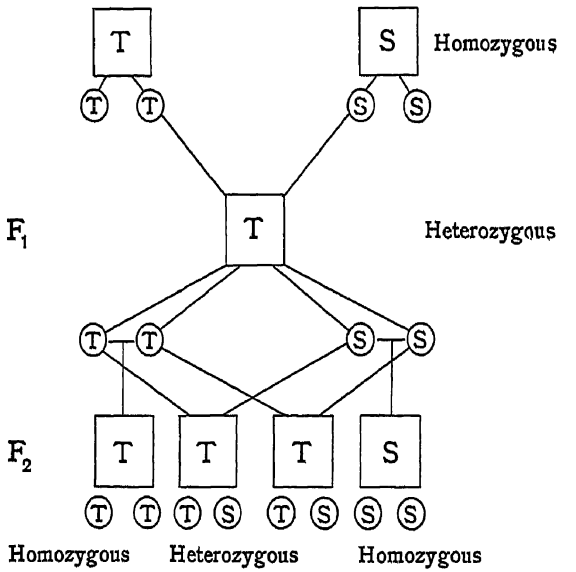


Fig 6.—To show the explanation of the results of crossing tall and short peas in the first and second generation according to the Mendelian laws of "*dominance*" and "*segregation*" Individuals are indicated by □ , gametes by O T, tall, S, short

they are now called, and that one of these pairs of characters is prepotent or dominant over the other This explains why in the first generation, F_1, all the plants are tall, since tallness is dominant to dwarfism

To explain the occurrence of tall and dwarf peas in the second generation, F_2, he concluded that the factors determining the characters are independently segregated and separated from one another

in the germ-cells—that a factor for tallness does not exist in the same germ-cell as the factor for shortness (Fig 6)

When he studied the heredity of more than one pair of characters Mendel found that in the pea the various pairs of characters which he studied are sorted independently of the others Thus he found that when tall peas with coloured flowers were crossed with short peas with white flowers the F_2 generation showed coloured to white in the proportion of 3 to 1 and tall to short in the same proportion That, supposing there were 16 plants, there would be—

12 tall	4 short
9 coloured 3 white	3 coloured 1 white

The segregation of the two characters was independent

Mendel's investigations remained unrecognised till they were rediscovered in 1890 The great extension of his work carried out since this date has shown that his results on peas may be applied to many other plants and to many species of animals, but that in its simple form it is not universally applicable

As the study of genetics has advanced, more and more happenings in heredity have been discovered which are inexplicable by Mendel's simple conceptions of dominant and recessive for each character, and of the absolute sorting out of these factors in the gametes, and all sorts of ingenious

hypotheses have had to be devised of the possible interaction of "factors" on one another, *e g* of the possible repulsion of factors for one another, of the development of "inhibitory" and even of "lethal" factors

But it must be admitted that many cases occur which do not follow the Mendelian laws Instances of inheritances from the mother alone are known in certain hybrids, but they, of course, are exceptions Morgan cites as an example the crossing of the fish *Ctenolabrus* with other species Intermediate forms of all grades may appear in the F_2 generation, as is seen in crosses of the Brown Leghorn and Silky fowls described by Punnett Further, heterozygous individuals may breed true, as is seen in the crossing of whites with negroes, with the production of mulattos which seem to produce mulattos Castle crossed lop-eared rabbits with the usual form and found that the F_1 animals were intermediate When a large rabbit is crossed with a small one the offspring are intermediate in size, and the F_2 generation shows no separation into large and small, as it should do according to Mendel's laws The speckled wood butterfly (*Parage egeria*) behaves in the same way when the brightly coloured southern form is mated with the pale northern form (Punnett) In these cases there seems to be no distinction of dominant and recessive

Cases also occur in which characters are not

strictly dominant and recessive, and in them the result of breeding can be explained only on the assumption that the dominance is merely partial Among well-known examples of this kind is the result of mating white-flowered and red-flowered samples of the common garden four-o'clock, *Mirabilis jalapa* F_1 shows pink flowers When these are mated together in F_2, white, pink and red flowers appear in the proportion of 1—2—1 A similar condition has been described in races of Andalusian fowls and in some forms of *Drosophila*—the fruit or vinegar fly Not only is this the case, but, as shown by Morgan, the dominance of a factor may be modified by external conditions, *e g* the character of feeding This he illustrates by the variation in the type of abdomen which appears in breeding *Drosophila* in different food conditions

Nor does the independent segregation of factors postulated by Mendel's law always take place

Bateson and Punnet found that when peas with purple flowers and long pollen grains were crossed with those with red flowers and round pollen grains these characters tended to come out together more frequently than in the ratio given above They therefore concluded that here there is not a free assortment of the factors, but that two of them tend to be linked

This idea of "linkage" of factors has been extensively used to explain departures from the normal Mendelian ratio in breeding experiments

But the fact that it varies from apparently complete linkage through all degrees to no linkage makes the application somewhat questionable

As will be seen later, it has been very largely used in explaining sex-linked characters, characters which pertain to one or other sex Morgan con-

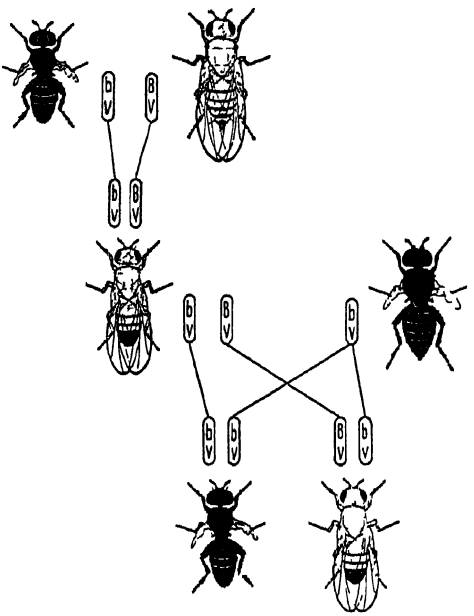


FIG 7.—To show "linkage" of characters as demonstrated in *Drosophila* by back crossing of a male of F_1 with a black vestigial female, in F_2 in equal number of black vestigial and ordinary "wild" flies appear (Morgan, by permission)

siders that these factors exist in the chromosomes of the gametes (p 37) Working on the fruit-fly, *Drosophila*, he uses back-crossing to demonstrate linkage If an ordinary wild fly is crossed with a variety, black with vestigial wings, the F_1 generation are all of the wild type, the characters of which are dominant, and if they interbreed the

usual proportion of wild to vestigial is produced But if a male of the F_1 generation be crossed back to a black-vestigial female, the F_2 generation shows wilds and black-vestigials in equal numbers This is said to indicate that black and vestigial wings are linked characters tending to come out together

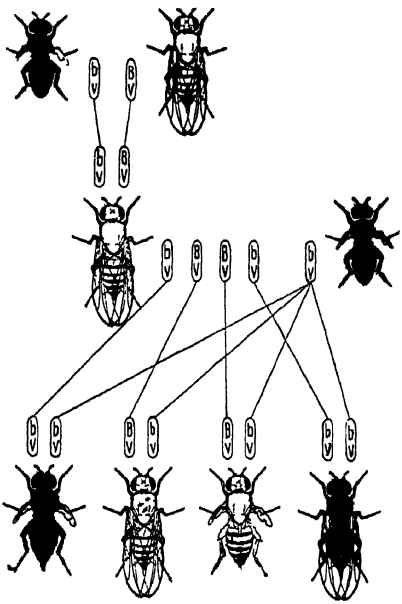


FIG 8 —To show "cross overs" as demonstrated in *Drosophila* by back crossing A wild female of F_1 is mated with a black vestigial male, and the F_2 generation is as shown (Morgan, by permission)

But instances occur in which the proportions in the F_2 generation cannot be explained by the linkage of factors alone Morgan cites the case of a wild fly crossed with black vestigial-winged, and giving in F_1 wild type flies If a female from these be mated with a male black vestigial, instead of two types appearing in the F_2 generation, four types appear (Fig 8) This he explains by an

exchange of factors in the germ cell, by a "cross-over" by which the vestigial, normally linked to black, parts with this and becomes linked to grey and *vice versa*. As we shall see later he supposes that this is brought about by actual changes in the chromosomes of the nucleus. He says "The percentage of cross-overs is definite *for a given stock of a given age and under given environmental conditions*" (the italics are mine), and he gives an account of the experiments of Plough in varying the percentage of "cross-overs" by varying the temperature at which the flies were kept.

Linkage and cross-over are ingenious hypotheses, and certainly the theory of *varying* amounts of "linkage" and *varying* proportion of "cross-over" greatly facilitates their application to the explanation of genetic results which do not conform to the original Mendelian law. Because it is possible to explain plausibly a happening in a particular way, that explanation is not necessarily correct. There are many examples of failure to show the clear cut differentiation expected in the F_2 generation. Morgan cites the case of the cross between the normal and bar-eyed *Drosophila*. The F_1 generation is intermediate. The F_2 generation shows all gradations from bar-eye to normal eye. Here the segregation does not seem to be complete.

Dominance then is relative, segregation not always complete, and true allelomorphs can be

claimed to exist only in those cases where the dominance is most marked, such as the pea If Mendelian inheritance were universally valid, the proportions of the distribution of any pairs of characters in the F_2 generation should always be manifest It is surprising that in so many cases it has proved to be so, but an elaborate statistical analysis which has been made of a vast series of most carefully collected data, namely that made by Udney Yule upon material collected by the late A D Darbishire, leads Yule to the conclusion "No explanation is offered of the remarkable divergences from the expectation based on simple Mendelian theory, they remain a puzzle But it seems clear that that theory is inadequate completely to explain all the facts The mechanism at work appears to be more complex than is commonly postulated"

Two views of the process of heredity seem possible

1st That the difference between gametes is *quantitative*, depending upon the relative prepotency of lines of chemical change in each of them That in fact the law of hereditary inertia is applicable

2nd That the differences are *qualitative*, depending upon the actual and definite sorting out of *factors* among them These factors may be definite lines of chemical change or definite structures determining the future line of development.

The findings of Mendel may be quite well explained on either hypothesis, and it is probably a gratuitous assumption that in the original tall and short peas each possessed only the factors of tallness and the absence of this, *i c* shortness, respectively

If dominance may vary to all degrees, and if it may be modified by changes in nutrition, if segregation also varies in degree it is difficult to understand how the factors are qualitatively different On the other hand the conception of the differences as quantitative differences in metabolism seems to explain the variations In the case of firmly established characters such as the tallness of certain peas, the line of metabolism of the germ in the tall plants is of a very high grade when compared with that of the germ of short plants, whereas in the case of the white and black races the difference between the grades of metabolism in the two germs is practically absent Where the difference is marked and distinct, as in the pea, the dominant character will manifest itself in the F_1 generation and will tell in the F_2 generation, so that a large proportion, three-fourths, are tall and only one-fourth short In some few of the tall the dominance of the line of metabolism may be so marked that in the F_3 generation a small proportion will be all tall, and it may be sufficiently weakened to allow another part of that generation to resemble the F_2 In

fact, if the metabolic difference is sufficiently marked the original Mendelian rule will be observed The various departures from the clear-cut difference will give rise to all the variations that have been recorded In short, inheritance

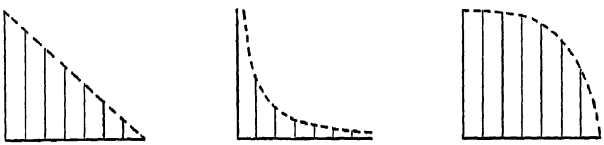


FIG 9—To illustrate how quantitative differences in the gametes may simulate qualitative In *a* there is a steady gradation, in *b* and *c* abrupt changes simulating differences in kind, in *b* in one direction, in *c* in the other

can be explained on the basis of the heredity of a definite line of metabolism (Fig 9)

The conception of absolute dominance, of complete segregation, and of the existence of definite allelomorphs led to an attempt to explain them by the theory that the chromosomes of the nucleus are the carriers of the factors

Before proceeding to consider this view it may be well to emphasize the point that heredity, breeding true, the result of what I have called hereditary inertia, occurs in forms where no definite chromatin structure obtains, and secondly that in forms where such structures do obtain the Mendelian laws are not always followed

It is well known that when a cell is about to divide a definite number of loops of chromatin, the chromosomes, emerge from the chromatin network of the nucleus, that they become arranged

round the equator of the spindles, that they split longitudinally and that a half goes to each pole of the spindle, so that when the cell divides each daughter cell has not only half the protoplasm but also half the chromatin of the mother cell (Fig 17, p 60) In sexual reproduction, before conjugation of the gametes occurs, a fusion of the chromosomes in pairs takes place so that their number is reduced to one half Hence when the gametes conjugate the original number of chromosomes is restored in the zygote, half being paternal and half maternal If the chromosomes carry the "factors," an explanation of heredity seems possible, but unfortunately it is impossible directly to demonstrate that they do so It was only natural, that when these visible changes were first demonstrated, attention should have been concentrated upon them and that they should be considered to be of primary importance, while the changes in activity which could not be made apparent should be relegated to a secondary place or ignored

The evidence relied on seems to be that, provided the factors are arranged along the chromosomes, provided that in splitting the originally fused chromosomes again separate, and provided that the chromosome before separating may cross over and exchange factors, then all the happenings of heredity are capable of explanation on a purely mechanical basis

The champions of the chromosome mechanism represent the "factors" in terms of these chromosomes as is seen in Fig 10, where the results of crossing the dominant long-winged fruit fly (*Drosophila*) with the vestigial-winged fly are represented by Morgan

Morgan cites as evidence of the relationship of the chromosomes to inheritance the fact that

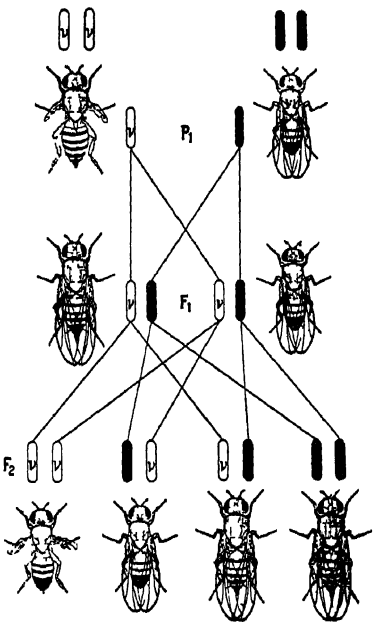


Fig 10.—To show the explanation of Mendelian inheritance on the chromosome theory (Morgan, *Crooman Lecture*)

certain "linked" characters of various species of *Drosophila* may be arranged in definite groups of two, three or more, and that the pairs of chromosomes in the germ cell correspond in number with the groups of characters

In *D melanogaster* the inherited characters of the

body may be arranged in four groups, and there are four pairs of chromosomes In *D Willistoni* three groups of characters have been described and three pairs of chromosomes In *D virilis* five groups of linked characters seem to occur and there are six pairs of chromosomes

Some of the groups of characters linked together are large, some small, and in these cases some of the chromosomes are large and some small Some of the characters are more closely linked than others This Morgan explains by each character being dependent on a definite part of a chromosome which he calls a "gene"—Mendel's "factor" reduced to a morphological entity He has actually attempted to calculate the probable size of a gene By the ingenious hypothesis of the transference of genes from one chromosome to another in crossing-over he has explained most plausibly various mutations of structure which take place in this fly

While one must accept the observations of such masters of technique as Morgan and his associates, one is justified in subjecting their interpretation of the results to critical examination, and it must be remembered that in these studies of changes in chromatin distribution the difficulty is that the process cannot be watched but that it has to be deduced from observations on series of fixed and stained specimens

If from generation to generation the groups of

characters peculiar to the species are due to the genes and the chromosomes containing them, it follows that these are eternal, going on as entities from parent to offspring What we know is that, in the process of preparation for reproduction, out of the convoluted network of chromatin fibres which are present in the resting nucleus, a definite number of characteristic separate chromosomes emerge, which unite in pairs to reduce the number to one half (see Fig 17), but whether this is simply the separation of chromosomes from the convoluted mass in which they have all along existed, or whether, generation after generation, as the result of the metabolism of the cells, the chromatin undergoes the same characteristic changes to produce the same number and arrangement of chromosomes, we do not at present know, and it seems unwarrantable to mark one of each pair of chromosomes as paternal and one as maternal in origin It is true that certain appearances in the nuclei of the cells produced from the zygote have been interpreted as giving support to the view that the individual chromosomes pass from one generation to another

For example, in *Ascaris megalocephala*, two chromosomes occur, and after mitosis and the reformation of the nucleus what appear to be their ends may be seen as prominences on the surface (Fig 11)

In some *Orthoptera* in the telophase condition

the chromosomes get enclosed in separate vesicles and undergo their changes in these But a compound nucleus is formed (*Locusta viridissima*) in the last division before reduction takes place

Evidence has also been adduced from the results of crossing two fish, *Fundulus heteroclitus* and *Menidia notata* The chromosomes of the former

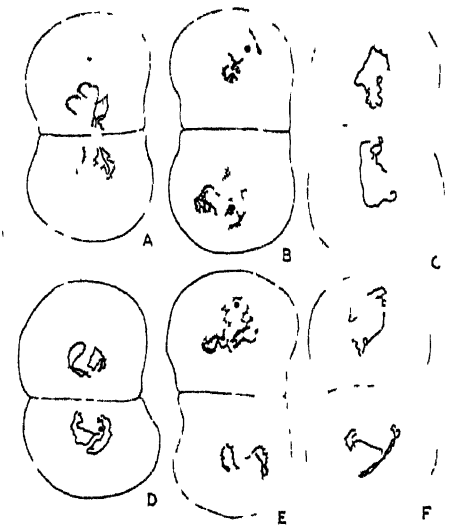


FIG 11 —The first division of the egg of *Ascaris megalocephala* to show the protrusion of the ends of the chromatin loops supposed to indicate their persistence (Boveri)

are long and straight, those of the latter short and somewhat curved After fertilization they fuse in the resting nucleus, but in the first mitosis they appear in two distinct groups in each of the cells In later divisions their identity is lost But it is manifest that if the chromosomes are the result of a line of metabolism imposed by each of the parents, it might be expected that the direction

given by each respectively would lead to the formation of chromosomes characteristic of each (Fig. 12)

It is well known that the chromosomes show marked differences in size and shape in the cells of different individuals of the same species, although attempts have been made to distinguish



Fig 12.—The persistence of the chromosomes of the parent gametes in the division of the zygote produced by crossing *Fundulus heteroclitus* with *Menidia notata* (Moenkhaus)

each particular chromosome in a series of germ cells These differences in shape must be an expression of differences in the metabolism of the nucleus or cell as a whole How far are the inherited characters the results of these metabolic differences and how far of the variations in the chromosomes ?

It must be recognised that the course of chemical changes in the protoplasm from generation to generation is as eternal as the chromosomes can

possibly be, but, while the latter are structures visible and manifest, the former is a process hidden and invisible

Even if the continuity of the chromosomes were proved it would not establish the theory that they are the determinants of the line of development and heredity, since, as already pointed out, the line is followed in living things in which definite chromosomes have not been demonstrated

With the usual conception of the chromosomes and their mode of action we should expect definite qualitative differences always to occur As already indicated this is not the case When the question of sex determination is considered it will be seen that there is further evidence of quantitative differences of effect which are more readily understood upon a kinetic than upon a static or structural basis

There is no doubt that if the mechanical theory be accepted it becomes possible to force it to explain all variations from the ordinary course in terms of changes in the disposition of the chromosomes But what is theoretically possible is not necessarily true, and a high degree of correlation does not necessarily imply causal relationship As Doncaster says, the antlers of the stag are closely correlated to its virility, but the factor determining both is the development of the testes The hereditary inertia of chemical change is probably behind the distribution of chromatin as

it is behind the development of all other structures It would be just as surprising to find a larva with the arrangement of spicules of echinus developing into star-fish as to find the zygote of a fruit fly that was going to develop into one form possessing the chromosome arrangement of another

Meantime it is sufficient to point out that configuration and arrangement of chromosomes may be an expression of a definite line of chemical change, that the chromosomes may be "the outward and visible sign of the inward and spiritual grace!"

The proof of this chromosome and gene theory of heredity is said to be of the same nature as the proof of astronomical theories, that from it it is possible to predict what will happen But if the chromosomes are merely an expression of lines of metabolism, the prediction is made from a sign and not from the cause of the sign

There is good evidence to show that factors other than the chromosomes act in determining the line of development M'Clung[1] cites experiments by Tennent on hybridisation of echinoderms in which he found that under usual conditions when *Hippnoe* was crossed with *Toxopneustes* the pluteı developed were always of the former type But if the hydrogenion concentration of the water were altered towards acidity, when Toxopneustes eggs were fertilized by Hippnoe sperms, the reverse occurred M'Clung adds (p 677) "It is indeed

[1] *General Cytology*, p 676

quite futile to attempt a separation of the parts of the cell functionally and to assign to one a particular type of character development and to another portion other characters Whatever there is in the cell *it is there because of the co-ordinated activities* of the cell as a unit" (The italics are mine)

Even Morgan admits that in some instances inheritance may be associated with other parts of the cells than the chromosomes, and cites the case of the spotted leaved four-o'clock If flowers on a green shoot are fertilized by pollen from a white shoot the plant produced is green, while if flowers on a white branch are fertilized by pollen from a green branch white leaved plants are produced

It is most interesting to find Johannsen[1] supporting the chemical view of inheritance He writes "We are very far from the ideal of the enthusiastic Mendelians, viz the possibility of dissolving genotypes into relatively small units, or the so-called genes, allelomorphs, factors or something else Personally I believe in a great central 'something' as yet not divisible into separate factors The pumice flies in Morgan's splendid experiments continue to be pumice flies even if they lose all 'good' genes necessary for a normal fly life, or if they be possessed with all the bad 'genes' detrimental to the welfare of this little friend of the geneticists" He says

"There is scarcely any doubt that Mendelian

[1] *Hereditas*, 1923, IV 133

factors are in some way bound up in or to the chromosomes," but he goes on

" In comparing an original organism with the undoubtedly cultivated organism, we might find that there is one single genotypical point of difference between them, this difference may probably consist in an alteration of the 'chemism' at a special point of the chromosome

" Such alterations may be more or less different, and where several differences exist in a certain locus of a chromosome we have the so-called multiple allelomorphs, polyallelism, these are different states (chemisms) in the same locus of the chromosome "

A criticism of the chromosome theory of heredity and of sex determination by Professor R Fick of Berlin appeared after the above was written, and the abstract given on p 106 should be read in this connection

Three possibilities have to be considered The two extreme views are, the first that the chromosomes are nothing more than an expression and result of a line of chemical change, the second that they are the carriers of the characters inherited and that they are the determinants of the lines of development An intermediate view may, however, be adopted It may be that the chromosomes are elaborated in order that they may act as stabilisers of the direction of hereditary inertia But, fundamentally, heredity depends upon the

transmission of a line of chemical change, as is shown by the inheritance of characters after division of cells in which the chromatin plays no manifest part

This brief consideration of the nature of life, of the manner in which living things become adapted to their environment, and of the influence of hereditary inertia in the transmission of characters from one generation to another shows that the study of physiology may conveniently be divided into the study of the activities of the somal cells —the *life of the individual*, and the study of the action of the reproductive or germ cells—the *continuity of the species* These, however, cannot be sharply differentiated since the germ cells and somal cells interact upon one another At present we are concerned with the problems of the continuity of the species

The student should read

1 Castle's *Genetics and Eugenics* Havard University Press 1924

2 Punnett's *Mendelism* Macmillan & Co , Ltd 1911 3rd edition

3 Morgan's *The Physical Basis of Heredity* Monographs of Experimental Biology Lippincott Co 1919

4 M'Clung, *The Chromosome Theory of Heredity General Cytology* Edited by E V Cowdry University of Chicago Press 1924.

CHAPTER II

REPRODUCTION

In the preceding chapter the significance of the hereditary inertia of metabolism has been considered in relationship to inheritance The necessity of division of living units, of reproduction, has been explained, and the various ways in which this is effected must now be dealt with

Reproduction or cell multiplication seems to be presided over by centres of activity which are indicated by the so-called *centrosomes* As Agar expresses it "The centrosomes are the dynamical centres of the cell" They and the rays which radiate from them to form the *aster*, or which get arranged as the *spindle* in nuclear division, are probably essentially centres and lines of activity in the protoplasm, which may of course be associated with changes in the consistence of the protoplasm They disappear and reappear, as is seen in the division of the non-nucleated fragments of the eggs of echinoderms (p 56), and they play a dominant part in the process of division They are manifestations of activity rather than morphological entities.

A AGAMETIC REPRODUCTION

1. **In Protozoa.** The most primitive form of reproduction is simple fission of the unit, and this may occur without or with preliminary changes in the nucleus, if that structure be present The former is known as *amitosis*, the latter as *mitosis*, and in unicellular organisms all stages between these have been described

Amitosis is seen in the simple fission of many infusoria, where the macro-nucleus appears to be divided into two parts without preliminary changes in the chromatin

In mitosis a break up of the nuclear network occurs, and separate masses of chromatin, the chromosomes, appear This process is undoubtedly dominated by the separation of the two centrosomes (Fig 17) and the formation of the spindle which lead to a rearrangement of the chromosomes and, after they have split, their collection round each centrosome In the typical form each loop of chromatin splits longitudinally into two, one part passing to one centrosome, the other to the opposite centrosome, so that when division is completed each daughter cell has identical centrosomes, protoplasm and chromatin

2 **In Metazoa.** In the body cells of most of the tissues of multicellular organisms cell division occurs either by amitosis or by mitosis

Another form of agametic reproduction is seen in the growing of buds and their separation from

the parent, as it occurs in *Hydra*, and by the division of the individual into two or more parts, as is to be observed in some sea worms

B GAMETIC REPRODUCTION

1. In Protozoa. As already indicated in the more complex of the protozoa, *e g Paramoecium*, a differentiation of the cell into a somal and a germ part has taken place, the micronucleus being the germ part (p 10) Reproduction may occur by division without the micronucleus being involved When conjugation takes place, the micronucleus undergoes important changes so that only one-fourth of the whole is transferred from one to the other of the conjugating individuals This may be considered as a primitive form of gametic reproduction Reproduction by fission may alternate with reproduction by conjugation, just as in the metazoa parthenogenesis in many cases alternates with sexual reproduction It is seen in the Foraminifera, where in the asexual form, in which the nucleus of the cell becomes multiplied by division, a mass of protoplasm accumulates round each nuclear mass to form a new individual These secrete shells and enlarge, and the nucleus divides into a somatic and a germ nucleus The latter breaks up into small masses of chromatin which escape as gametes, each surrounded by a little protoplasm, and they conjugate in pairs, and the zygotes then form an asexual generation

2. In Metazoa. In the metazoa, where the germ cells are distinct from the somal cells, true gametic reproduction occurs This may start without or with conjugation The former process has been called *parthenogenesis*, and here the inheritance is from one parent only, the latter involves the process of *fertilization* or conjugation of gametes either produced in the same or in separate individuals when inheritance is from both parents

1. Parthenogenesis. Parthenogenesis occurs in many of the metazoa, even in those so complexly adapted as the insects Under some external conditions parthenogenetic reproduction in certain forms may go on almost indefinitely But it very frequently alternates with sexual reproduction, as in the Aphids (Gall-flies) and in Rotifera

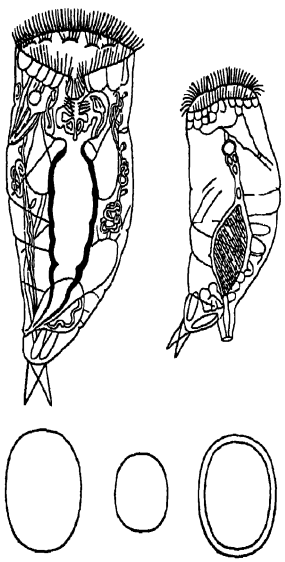


FIG 13.—*Hydatina scuta* and its eggs The larger female and smaller male are shown above The eggs, more magnified, are shown below from left to right the parthenogenic female producing, the parthenogenic male producing, and the fertilized thick shelled winter egg (From Doncaster)

In *Hydatina*—a Rotifer—males and females are produced, but generally the males are small and functionless, although they pair with the females they produce no effect unless it be with a very young female, which would parthenogenetically produce a male, in which case

fertilization is effected and large eggs with thick shells are produced—the "winter eggs"—and these yield females (Fig 13)

Although the nuclear changes in parthenogenesis have not been so fully investigated as in the case of sexual reproduction, the observations made seem to show that generally from the convoluted mass of chromatin in the nucleus a definite number of separate loops, the chromosomes, are developed and the egg divides by the ordinary process of mitosis and forms one polar body The ovum then divides, and again divides to form the morula This occurs in some Ostracods

In some parthenogenetic animals (*Artemia*) the polar body returns into the egg and reunites with the nucleus

In parthenogenesis, by the law of hereditary inertia, it would be expected that either parthenogenetic individuals or sexual females would be produced But in *Artemia* and in some Phyllopods males are also formed This will be considered under the determination of sex (p 79)

In certain cases where the egg may develop either parthenogenetically or after fertilization, *e g* in the Honey Bee, the chromosomes when formed conjugate in pairs, thus reducing the number to one half If the egg be fertilized the original number is restored and a female is developed If it is not fertilized a male develops, and the reduced number persists in the cells In

the nucleus may divide as if to form another, and then the two nuclei may again fuse, restoring the number of chromosomes This corresponds to what has been described in the parthenogenesis of *Artemia* (p 53)

The study of chemical fertilization has thrown light upon the nature of the centrosome and its related spindle In normal impregnation the centrosome of the egg disappears and another is introduced with the sperm But in artificial impregnation fresh centrosomes are formed in the protoplasm of the egg In fact, Wilson and M'Clendon induced segmentation in bits of the eggs of *Asterias* in which no nucleus existed, division centres or centrosomes being formed before each division

The experiments on chemical fertilization seem to indicate that the whole process of the development of the gamete on the lines determined by hereditary inertia is simply the result of chemical changes arising from alterations of the surroundings, or, as we shall presently see, from changes due to the invasion of another body

3 True Fertilization. The question of how the development of the ovum after fertilization—the conjugation of the whole or parts of two germ cells—is related to natural and to artificial parthenogenesis must next be considered

The most characteristic part of the fusion of two germ cells is the fusion of their nuclei to form a single nucleus (Figs 20 and 21)

the subsequent development of sperms in the adult drones no reduction of the chromosomes occurs

Whether reduction of chromosomes does or does not occur, the nucleus and the cell divide and subdivide, differentiating into the gametic cells for the production of succeeding generations and the somal cells for nourishing and protecting these The somal cells undergo their further development on definite lines as a result of hereditary inertia

What initiates the process of parthenogenetic division is unknown But, since evidence will be adduced to show that chemical changes, induced either by the introduction of a sperm or by altering the chemical state of the environment, may start the development of the eggs of some animals, the conclusion seems fair that some chemical change, either resulting from the growth of the ovum or due to changes in the tissues or fluids surrounding it, must start its development

2. Chemical Fertilization. Closely allied to this true parthenogenesis is the development of the ovum under the influence of chemical changes in the environment which has been so elaborately studied by Hertwig and subsequently by Jacque Loeb, first in the eggs of echinoderms and later in the eggs of the frog

One method consists in exposing the egg to a solution of one of the lower fatty acids such as butyric acid This leads to the formation of a

fertilization membrane round the egg and to an increased consumption of oxygen by the egg, and possibly to one or two divisions of the cell But, if the egg be now placed in a hypertonic salt solution, under suitable conditions, the nuclear membrane disappears and typical divisions of the nucleus and of the ovum occur, which may proceed to an advanced stage of development In some cases frogs with complete metamorphosis have been obtained, and of these some were male and some female In the males spermatogenesis is stated to have proceeded without reduction of the chromosomes



FIG 14.—Chemical fertilization of the egg of the frog 1 and 2 The young frogs produced 3 The ovary of one of these (J Loeb)

The eggs of Echinoderms undergo the maturation process—the halving of the number of chromosomes—before the application of the chemical stimulus, and hence the cells of the new individual have a decreased number of chromosomes.

On the other hand, if the egg does not normally mature until the sperm has entered it (*Thalassema*), then, when division is artificially induced, it undergoes a process of reduction before it divides In some cases only one polar body is thrown out, but

the nucleus may divide as if to form another, and then the two nuclei may again fuse, restoring the number of chromosomes This corresponds to what has been described in the parthenogenesis of *Artemia* (p 53)

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But in certain cases it has been found that the sperm nucleus does not fuse with the nucleus of the ovum, but that it disintegrates Nevertheless multiplication and development of the ovum take place This is strikingly illustrated by the artificial fertilization of sea urchins' eggs by the sperms of a mollusc which produces division and development, although the sperm nucleus plays no part in the process, and a typical sea urchin is formed

In *Rhabditis aberrans* the egg nucleus undergoes no reduction division to decrease the number of chromosomes, but a sperm must enter the egg before division, its nucleus does not, however, unite with the female pronucleus, and finally degenerates, and the ovum goes on dividing and developing

On similar lines is the observation by Hertwig that when toads' eggs are brought into contact with frogs' sperms very few are fertilized, and these do not reach the gastrula stage When the sperms have been first subjected to radium emanations a large proportion of the eggs develop past the hatching stage

Apparently some chemical action of the sperm is the prime factor in starting division of the ovum This is indicated by the formation of a fertilization membrane and by the enormous increase in the consumption of oxygen by the egg on the entrance of the sperm The conjugation of the nuclei,

important as it may be in the inheritance of the characters of the two parents, is of secondary moment

While the initiation of the chemical changes which lead to division must be regarded as the

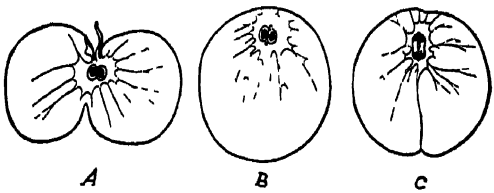


FIG 15.—Conjugation of two cells of equal size in *Noctiluca* (Ishikawa)

primary action of conjugation of the gametes, the fact that, in cases where the conjugating gametes

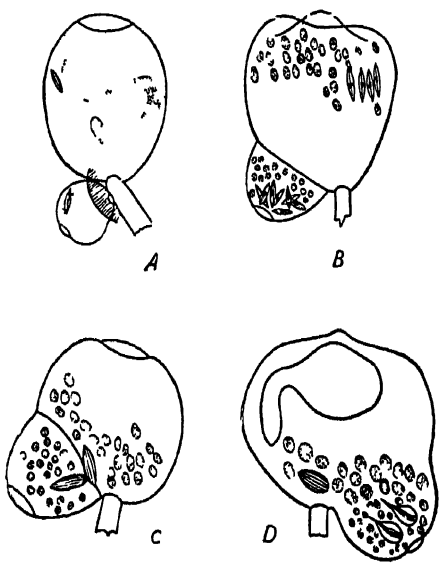


FIG 16.—Conjugation of two cells of unequal size (*Vorticella*) A large fixed macrogamete and a small microgamete (Maupas)

are the product of two separate individuals, the future history of the zygote is determined by

the previous history of *both* parents, has led to the attention of investigators being largely directed to the study of the effects of this combination upon the characters developed in the offspring

As we have already seen in protozoa there may be a complete fusion of the two entire cells, or there may be simply an exchange of part of the nuclear substance

Even in protozoa, *e g* in the infusorian *vorticella*, the conjugating cells may be of two kinds, one large—the macro-gamete—the equivalent of the ovum, and one small—the micro-gamete—the equivalent of the sperm (Fig 16)

In all higher animals this differentiation of the two cells is universal, the large gametic cell being the ovum, the small gametic cell the sperm

Maturation. In the gametic cells, from the chromatin of the resting nucleus a definite number of separate masses of chromatin, characteristic of each species, the chromosomes, make their appearance, and these generally are arranged in similar pairs (Fig 17)

In the process of preparation for conjugation, the process of maturation of the ovum and of the sperm, these pairs conjugate, and the number is thus reduced to half

In the *sperm* after the conjugation of the chromosomes a spindle forms, and each chromosome divides again so that the original number is

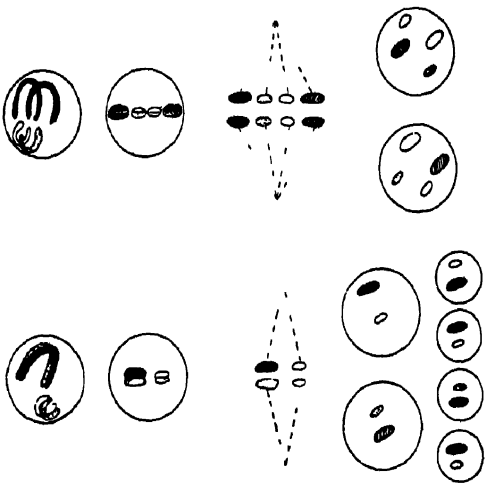


FIG 17.—Simple scheme of ordinary mitosis and of fusion of chromosomes in maturation of gametes to reduce the number to one half. (From *General Biology* by Burlingham, Heath, Martin and Pierce. Published by Jonathan Cape, London 1923.)

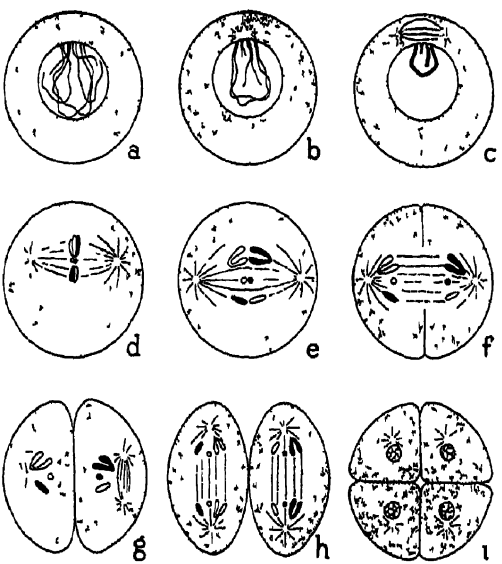


FIG 18.—Maturation of sperm cell and the formation of four spermatocytes. (Morgan, *Croonian Lecture*.)

restored One half of these go to one centrosome, the other to the other, and the cell divides. Then immediately another spindle develops and the chromosomes split, and half goes to each pole and the cell divides so that four cells are formed from the original one, and each of these contain half the original number of chromosomes (Fig 18)

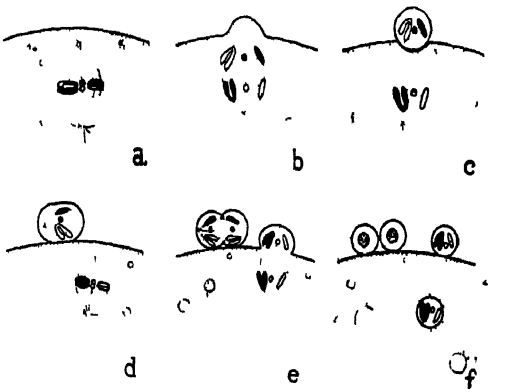


Fig 19.—Maturation of the egg cell and formation of an ovum with three vestigial polar bodies (Morgan, *Croonian Lecture*)

In the *egg* the conjugated chromosomes split, and one part moves or is moved to each pole, and then one half of them is passed out into a polar body which is really a small cell In this they divide in the usual way and form two cells The chromosomes left in the egg again split, and again one member of each pair passes out in the second polar body, and the original nucleus is thus left with half the original number of chromosomes Four cells are formed, of which three are vestigial—only one, the ovum, is of importance (Fig 19)

Conjugation. Conjugation or Syngamy consists in the entrance of the spermatozoan into the ovum and the union of its nucleus with that of the ovum

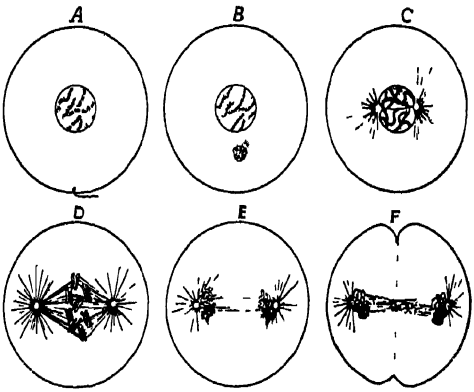


FIG 20.—Simple scheme of syngamy (Same source as Fig 17)

Before conjugation of the nuclei, the centrosomes of the ovum have disappeared and a new centrosome appears in front of the sperm nucleus

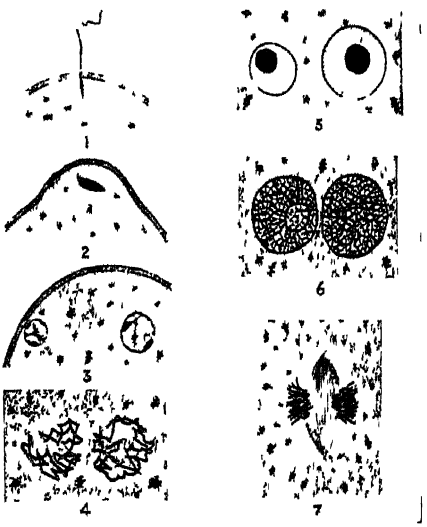


FIG 21.—Syngamy in the egg of the mouse (Sobotta)

The nuclei, when they unite, generally come together in the resting phase and mitosis then occurs (Figs 20 and 21)

The time of the entrance of the sperm in relation to maturation of the nucleus of the ovum varies in different species, and the condition of the nuclei at the time of fusion also varies, but essentially the process is as described

The most striking chemical change in fertilization is the enormous increase of the oxygen consumption of the egg Shearer[1] finds that the mere contact of the sperm with the ovum produces an increase which may amount to no less than 8000 per cent ! A later and smaller increase seems to be correlated with the passage of the sperm into the cytoplasm

The consideration of the phenomena of reproduction emphasizes the importance of the protoplasm with its centrosomes and their rays, the part played by the chromatin of the nucleus appears to be a secondary and more or less a passive one

The chromatin must be considered as an anabolite of protoplasmic activity, an anabolite transmitted from one generation to another, but even in the germ plasm augmented in each generation In its increase and in its distribution it follows the course of hereditary inertia, and its action in each genera-

[1] *Proc R S* 1922 B 93, 213

tion may be (1) to stimulate the chemical changes that lead to division and multiplication, and (2) to stabilise the direction of chemical change which determines development on ancestral lines

The relationship of parthenogenic to bisexual reproduction is further discussed on p 82

CHAPTER III.

SEX

THE germ cells of a zygote or of a parthenogenic ovum develop into ova and sperms either at the same time, or at one time into ova and at another into sperms, or they may all develop into ova or all into sperms Whatever their future development they are at first indistinguishable and have been called *primitive gonocytes*.

When ova and sperms develop in the same individual the condition of hermaphroditism exists, and this, as indicated, may be simultaneous or consecutive, when they develop in separate individuals true bisexualism occurs Even in sexual forms there is often a tendency to revert to the hermaphrodite condition

Hermaphroditism is very common in many groups of invertebrates, and it also occurs in some vertebrates

It varies in all degrees from true unisexualism to bisexualism and the two conditions may alternate in the same species

In many invertebrates, *e g* in the barnacles, ova

and sperms are produced at the same time in the same individual But, in many cases at least, self-fertilization does not occur, the ova apparently being immune to the sperms of the same individual and capable of fertilization only by sperms from another In several species, in addition to true hermaphrodites, small imperfectly developed males and in some complete females exist There is evidence that the course of development into males, hermaphrodites, or females, depends upon the environmental condition Geoffrey Smith finds that if the free-swimming larva settles in a position in which it can grow to its full size it develops into a hermaphrodite, or even into a female On the other hand, when the larva fixes itself to a female, it becomes a stunted male

The production of sperms at one period of life and ova at another is very common among the crustacea The parasitic isopod *Bopyrus* is male when young and becomes female later

In many animals, where both sperms and ova are formed, one process may be in abeyance Thus, in the male frog a structure known as the organ of Bidder which lies in front of the testes is an undeveloped and functionless ovary Pouse[1] found that after castration of male toads the organ of Bidder may produce ova which may be fertilized and produce normal tadpoles Harms[2] states that

[1] *C R Soc Biol* 1925, 92, 522

[2] *Ztsch f Anat u Entwickl* 1923, 69, 598

in toads removal of the testes and over-feeding with fatty foods and lecithin leads to the formation of normal ova in Bidder's organ, and even to the development of the female internal genital arrangement Again, frogs occur with gonads neither definitely male nor female This condition will be considered later

The Hag-fish (*Myxine*) is said to be male when young and to become female later It possesses an ovotestis in which the formation of sperms and ova varies greatly in different specimens

In amphibia sex appears to be peculiarly labile Witschi[1] records a number of observations on modifying the sex by external conditions, which will later be considered under "Determination of Sex," and he concludes that the line of development, which the germ cells in the developing gonad will follow, depends upon the position they take up in the gonad, and that the Leydig's cells in the sexual cords determine the development of sperms

Champy[2] records the observation that in the newt, *Triton*, spermatogenesis may be prevented by starvation, and that the testes may become replaced by fat in which undifferentiated gonocytes occur On feeding two such males they assumed the external characters of the female

[1] *Ztsch f indukt Abstam u Vererbungsl* 1922, 29, 31, Abstracted *Berichte u d Physiologie*, 1924, 22, 363.

[2] *C R Acad. Sc Paris*, 1921, 9th May

In one, in the place of the testes, was an immature ovary with oocytes A typical oviduct was enclosed in the structure

Guyénot and Pouse[1] have described several cases of sex reversal in toads, one in which a male which had fertilized eggs of a female was castrated and subsequently produced fertile eggs

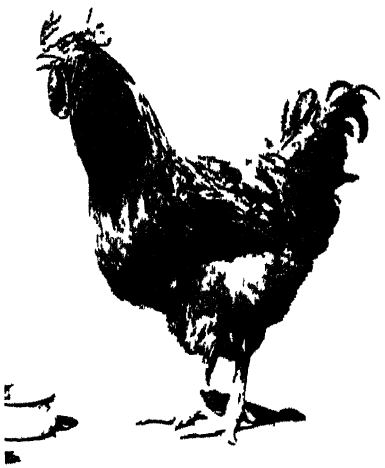


Fig 22 —Sex reversal in the fowl Cock which had previously been a hen (Crew)

F A E Crew[2] has described several cases of various degrees of sex reversal in the fowl, all showing a more or less complete transformation of the female to the male One of these, a Buff Orpington, which had been a typical hen, a good layer and the mother of chicks, at the age of $3\frac{1}{2}$ years gradually changed in all its character to a

[1] *C R Soc Biol* 1923, 89, 129

[2] *Proc R S* 1923, B 95, 256

cock, developing the male plumage, spurs, wattles and comb, crowing lustily, fighting other cocks and treading hens Mated with a virgin hen two of a series of eggs were fertilized and hatched out The bird died, and on post-mortem examination a tubercular tumour of the ovaries involving also other organs was discovered Alongside of this typical testicular tissue in which spermatogenesis was going on and two vasa deferentia were found

In the other cases lesser degrees of structural and functional sex-reversal were found In all there was degeneration of ovarian tissue and the fresh growth of peritoneal epipthelium to form semeniferous tubules

An interesting confirmation of such changes of sex is afforded by experiments of Benoit on the fowl [1] After performing ovariotomy he found that an organ had developed on the right side having the character of a testes with imperfectly developed tubules, spermatids and spermatozoa and with characteristic interstitial cells

Such observations show that in many cases of reversal of sex not only does the character of the gametic cells alter, but the course of metabolism and growth of the somal cells also changes This is still more clearly seen in the spider crab *Inachus*, which is male, producing sperms, before it is full grown, and at this time has the typical body-form of the male with large claws and small tail

[1] *C R Acad Sc* 1923, 177, 1074-1243

Later the testes become reduced and the body-form becomes of the female type Still later, however, the testes again enlarge, and the animal again develops the large claws characteristic of the male (Fig 24)

That sex may be determined by the influence of environment is shown by the life-history of the marine worm *Bonellia* In this animal there is the most extraordinary difference between the female and the male The former is large, with a barrel-shaped body and long proboscis The male is minute, with all its somal organs degenerated, and it lives in the excretory ducts of the female Whether a young individual will develop into a male or a female depends upon whether or not it settles upon the proboscis of an adult female, if it does so it becomes a male That this is due to the influence of the female is shown by the fact that if the young males be removed early they will develop into females, if later into a hermaphrodite or intersexual form, and if still later they will remain males If it settles on sea bottom it develops into a female



Fig 23 —Female of *Bonellia viridis* reduced to about one quarter the natural size The male might be represented by a small dot (From Doncaster)

Generally speaking, a good state of nutrition is associated with the development of ova and of

the female type of body, as is seen in some of the barnacles The supply of nourishment may thus modify the nature of the germ cell and, since it is through the somal cells that the gametes are nourished, there is thus evidence that the somal cells can and do act profoundly upon the gametic cells, and that Weismann's conception of the entire independence of the somatoplasm and the germ-plasm cannot be accepted Further evidence of this action will be cited later

Most higher animals are bisexual, sperms are produced in one individual, the male, and ova in another, the female, and the sexes generally differ from one another not only in the character of the gametes but also in the metabolism and in the structure of the body, especially in the secondary sexual organs

The differences in the metabolism of the male and female somata are very strikingly shown in some invertebrates

Thus Steche found that in some moths the blood of the female was green while that of the male was yellow, and that the precipitin tests showed as marked a difference between the blood of the two sexes as between that of the same sex in different species

The normal changes in the sex of the spider crab *Inachus*, with its changes in metabolism and structure, have already been described (Fig 24) Geoffrey Smith finds that in the female the blood

is very rich in fatty substances, which are used in the production of the yolk of the eggs When the tissues of the male crab are invaded by the parasite *Sacculina*, the testis, even if not invaded, degenerates, and the crab assumes the body-characters of the female This change was at one time assumed

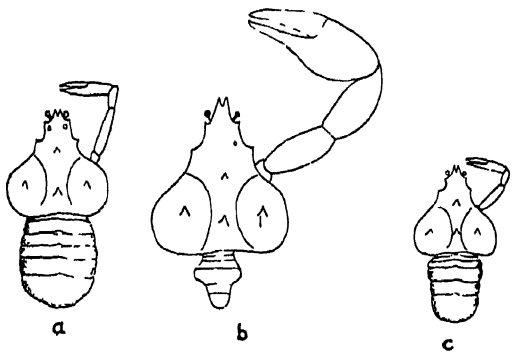


FIG 24 — *Inachus* (*a*) Adult female (*b*) Adult male (*c*) Male castrated by sacculina (G Smith)

to be the result of the removal of the influence upon the body of an internal secretion of the testis, but it may be due to the sacculina using up the fatty substances present in small amounts in the blood of the male, thus stimulating their increased production, and in this way, by modifying the metabolism of the soma, directly leading to the development of the female structure In fact, the production of ova and the female structural characters may both be the result of a special type of metabolism—a special kind of chemical change

In the human subject similar differences in metabolism and body structure of male and female are manifest In the female the rate of

chemical change, as measured by the basal metabolism, is lower than in the male In the adult male it is equivalent to 40 calories per sq metre of body surface per hour, in women to 37 calories In the female there is also the greater tendency to the deposit of fat, especially in the breasts and buttocks The bones, too, are more slender than in the male and the muscles are less strongly developed The condition of the larynx and the distribution of hair is different

The development of a special type of gamete with a special metabolism and the existence of a type of body corresponding to it may thus be regarded as linked characters in the Mendelian sense

But, while these differences exist between the two sexes, it must be remembered that the line of demarcation is not a hard and fast one, and that, as we have just seen, one sex may change to the other, and that, as we shall shortly see, intersexual forms occur As everyone recognises there are manly women and womanly men both physically and mentally Extreme cases of this kind are to be seen in the somewhat rare condition of pseudo-hermaphroditism in the human subject, where the dissociation of gonadal and somal sex is very complete

Quinby of Boston[1] has published clinical and histological reports of two such cases

[1] *Endocrinology and Metabolism*, vol 2, p 229 (D Appleton & Co , New York and London, 1922)

One is that of an apparent boy (Fig 25) of ten with hypospadias testes were not apparent Upon



Fig 25 —Dissociation of gonadal and somatic sex in an apparent boy (Quimby)

operation an infantile uterus with tubes and ovaries of normal appearance were found (Fig 26)



Fig 26 —Ovary from case shown in Fig 25 (Quimby, *Endocrinology and Metabolism* Published by D Appleton & Co, New York)

The second case is that of a negress of seventeen years of age, with all the external characters of a female (Fig 27) There was a vagina but no



Fig 27 —Dissociation of gonadal and somal sex in apparent girl (Quinby)



Fig 28 —Testes from case shown in Fig 27 (Quinby)

uterus or Fallopian tubes In the right groin a rudimentary undescended testicle was found (Fig 28)

Russell Andrews records the case of a well-formed woman with a short vagina but no uterus, in whose abdominal cavity two testes, as determined by microscopic examination, were found

Closely related to the dissociation of sex in man is the inter-sexual condition of true hermaphroditism in which male and female gonads are present in the same individual

Sand[1] records a case in a child of ten which was considered to be a male and presented the appearance of an undeveloped boy of that age There was a short vagina, a clitoris and labia, and in the right labium a testicle could be felt The inguinal canals were opened On the right side a testicle and lying deeper an ovary were found, on the left side two testicles An underdeveloped uterus was present Small bits of the testes and ovaries removed for examination had the histological characters of glands in an early stage of development

The only explanation which can be offered of the definitely unisexual character of the body in the presence of male and female gonads is that during the period of development of the secondary sexual characters the activity of one or other type of gonad has preponderated

One form of intersexuality is the unilateral type which has been observed in some birds Bond has described an interesting case of this kind in a pheasant which had male somal characters on the one side and female characters on the other, and which possessed a single ovo-testis (Fig 29)

Recently Pezard, Sand and Caridroit[2] have described the experimental production of such unilateral sexual differentiations of plumage by castrating pullets and then removing the feathers on one side in the regions where sex characters

[1] *J d'Urol* 1923, 15, 171

[2] *C R Soc Biol* 1923, 89, 1103

are marked. They state that feathers of the male type grow in the place of those removed

A functional as well as an anatomical dissociation of sex may occur, the individual being attracted to members of its own sex (*Homosexualism*)

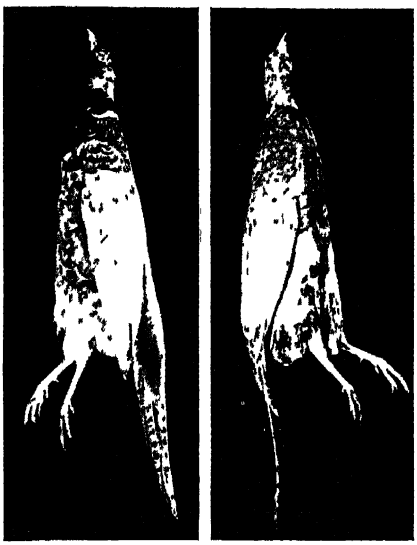


FIG 29.—Unilateral type of intersexuality in a pheasant one side shows plumage of cock, the other side that of hen (Bond)

Steinach has investigated the histology in some of these cases In a goat with female external genitals and bodily form but with the sexual behaviour of a male he found ovo-testes In five homosexual men he found the absence of spermatogenesis and two distinct types of interstitial cells, one resembling those of the testis, the other larger and with the appearance of ovarian interstitial cells

Physiologically of even greater interest are certain curious cases of alternations in the sex instincts

Historically one of the best known is that of the Chevalier d'Éon de Beaumont, born in 1723 It seems never to have been discovered what were the characters of the secondary sexual organs but, after being treated as a man, he went as a woman on a diplomatic mission from Louis XV to Elizabeth, Czarina of Russia, in 1756 During the Seven Years' War he was a Captain of Dragoons, but in 1777 he again assumed the dress and character of a woman, and died in London in 1810[1] Aldous Huxley, in his *Limbo*, describes a similar condition

The explanations of these conditions and of the reversal of sex must be postponed till the interrelationship of the gonads and soma has been considered (Chap VI)

A study of the origin of the sperms and ova shows that the differentiation of two sexes is by no means so marked as is generally supposed, that both forms of germ cell may be produced by one individual, that an individual may at one time have the characters, gonadal and somal, of the male and at another of the female, and that the gonadal sex may be dissociated from the somal Lastly, there is evidence that gonadal and somal sex may be influenced by environmental conditions This leads to the consideration of what are the factors which determine and modify sex

[1] A Lang, *Historical Mysteries* (Thomas Nelson & Sons), p 294

CHAPTER IV

THE DETERMINATION OF SEX

In the previous chapter the frequent occurrence of parthenogenesis and of hermaphroditism, the absence of any hard and fast line between male and female, and the not infrequent transformation of the one sex into the other have been pointed out The influence of environmental conditions in determining and modifying sex has been indicated by the life history of *Bonellia* (p 70) In short, the lability of sex has been emphasized

But in a large number of animals the two sexes differ from one another both in the character of the gametes (gonadal sex) and in the physiology and structure of the body (somal sex), although cases of dissociation of these have been referred to (p 74)

What then determines the character of the sex of the individual into which any given egg or zygote will develop ?

A **Parthenogenic Organisms.** It might be expected from the law of hereditary inertia that the offspring of parthenogenic females should be par-

thenogenic females But, while in some forms parthenogenic reproduction goes on uninterrupted for many generations, under certain conditions sexual forms are produced, and these may be female or male Generally one set of individuals produce eggs developing into females, another set those developing into males, but in some cases at least the same individual may produce both females and males There is considerable evidence that the onset of the production of sexual forms is determined by nutrition

Both in water-fleas and in the rotifer, *Hydatina*, rich nutrition favours the continuance of parthenogenic production of females, while starvation and cold seem to favour the production of males

It would seem as if good nutrition of the individual determines the production of ova rich in nourishing material which develop into parthenogenetic females, while bad nutrition leads to the formation either of females producing ova no longer capable of parthenogenetic development, but requiring the stimulus of syngamy with a sperm, or into males producing germs with a still smaller supply of nourishment—the sperms—incapable of development, but serving, when they conjugate with an ovum, to stimulate development in it

Consideration will later be given to histological investigations indicating that differences may exist between the distribution of chromosomes in the

germ cells producing males and those producing females

In the parthenogenic Aphids Morgan and von Baehr found that in the eggs which will develop into females there is no maturation process, but that the chromosomes, which are of even number, split normally into two In the male-producing eggs one chromosome does not split but is extruded and thus an odd number of chromosomes is left. The tendency to maleness or femaleness is thus here correlated with a particular distribution of chromosomes. But what determines the development of any given set of gametes in the one direction or in the other we do not know, and it does not really help to say that the one set is male because they contain an odd chromosome and the other female because they contain an even number We must go further back and enquire why this distribution of chromosomes arises it can only be as a result of some difference in the metabolism of the two sets of eggs

Further, the explanation of why in Aphids all the fertilized eggs develop into females is not easy If, as in *A salicetı*, the ova have six chromosomes before maturation and the sperms five, in the process of maturation, two kinds of sperms, one with three and one with two chromosomes, should be formed—one female-producing and one male-producing The explanation given is that the sperms with two chromosomes die [1]

B **Hermaphrodites.** The question of sex determination is here not involved, since each zygote develops ova and sperms, but the transition of hermaphrodites into bisexual forms and *vice versa* must be remembered.

C **Bisexual Organisms.** The passage from parthenogenic reproduction to sexual reproduction appears to have been a gradual one

The evidence considered seems to show that, as a result of impaired nutrition the eggs produced are no longer capable of developing into perfect female-producing parthenogenic eggs, and a progeny results, some of which produce sperms entirely incapable of development, but which yet have the power when conjugating with a less degenerated germ cell to stimulate it to division and development, and others which produce less degenerate gametes, the ova The former individuals are males, the latter females The result of the syngamy of the germ cells of these may produce a zygote which may develop into a parthenogenic female, or sexual reproduction may be continued in the next generations In that case the oocytes no longer develop into ova capable of spontaneous division, a peculiar fusion of chromatin loops precedes division, and only one in four of the cells formed is capable of fertilization and development The other three remain atrophic as the polar bodies

The spermatocytes show the same fusion of

chromatin loops before division, so that each has but half the normal number, and there is a tendency to the development of asymmetry

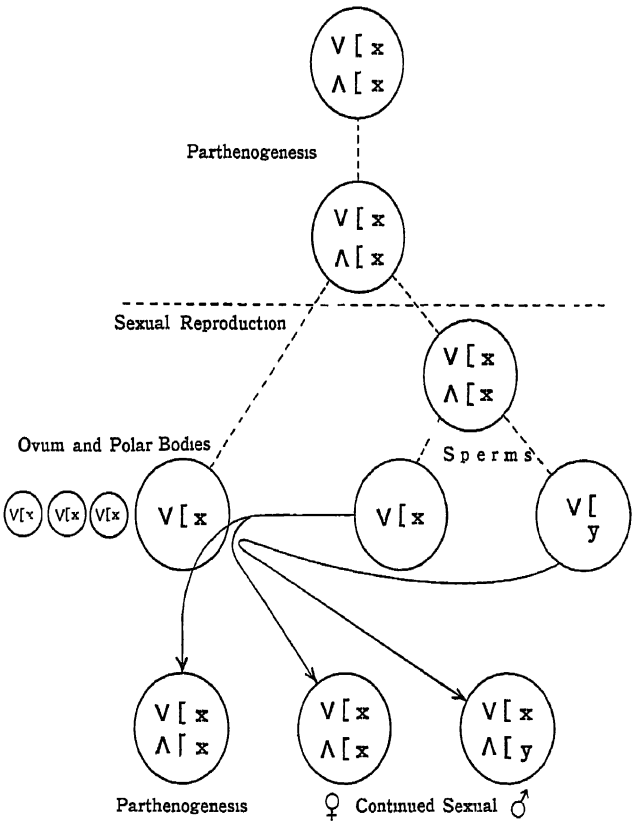


FIG 30 —Scheme of the probable development of sexual reproduction from partheno genesis The chromosomes are indicated diagrammatically as V[x V[x

The transition from parthenogenesis to sexual reproduction may perhaps be illustrated by the accompanying figure (Fig 30)

When sexual reproduction is established the sex of the individuals produced may be determined in various ways

Each egg and sperm, derived as it is from the conjugation of a previous egg and sperm, should possess a metabolism both in the direction of femaleness and in the direction of maleness These might be equally developed in each egg or sperm, or one tendency might be more manifest in some eggs and in some sperms than in others There might be a *grading*, so that some eggs had a more marked tendency to femaleness than others and some sperms a more marked tendency to maleness, and this grading of potency might be better marked in the eggs or in the sperms or it might be equally prominent in both

The grading might be more or less abrupt, and if disposed as in *b* and *c* the differences might be so marked as to stimulate quantitative differences (Fig 9 p 37)

The evidence undoubtedly points to the differences being preponderant in the eggs in some few species and in the sperms in most, and these differences are so marked in some cases that observers have concluded that they are not merely *quantitative*, but actually *qualitative*—that some eggs are of one kind, female-producing, and others of another, male-producing, and that some sperms are male-producing and others female-producing

The evidence that in some cases the difference is in the eggs and in others in the sperms may now be considered, and cases where the differences are

in the eggs, where sex is determined before fertilization, may first be dealt with

The genetic study of sex-limited inheritance affords examples of this

In one breed of fowl known as the Barred Plymouth Rock it has been found that, when a hen is fertilized by a cock of some other breed, all the male chicks develop the barred marking but the females do not The only possible explanation seems to be that different grades or kinds of eggs are produced, in some of which maleness is associated with the metabolism which leads to barring, in the others of which femaleness is not associated with such barring

In the currant moth there is the same evidence The common variety is known as *Abraxas grossulariata,* and it varies greatly in its markings But there is a distinct variety, paler and with quite different markings, known as *A lacticolor*

When a pure *A gross* ♂ fertilizes an *A lact* ♀ all the progeny are *A gross* The male transmits the *gross* character to all its offspring

When *A lact* ♂ fertilizes a *A gross* ♀ then all the ♂ progeny are *gross,* all the ♀ *lact* (Fig 31)

The simplest, although not the only possible explanation, is that the ♀ must produce some gametes which react to the *A gross.* sperm in one way and which are male-producing, and others which do not react and which are female-producing There must, in fact, be different grades or kinds of eggs

The *A gross* ♂ transmits the *gross* markings to ♂ and ♀ offspring alike, but the *A gross* ♀ transmits them only to her sons

The inheritance is here also limited to sex

In mammals and in many insects the evidence of sex limited inheritance points to there being differences in the sperms, some producing or tending to produce males and others producing or tending to produce females

This condition has been most elaborately worked out by Morgan and others in the fruit-fly, *Drosophila* Normally it has red eyes, but some white-eyed males were found and white-eyed females were bred

It was found that normally a white-eyed ♂ with a red-eyed ♀ gave both sexes red-eyed, but that red-eyed ♂ with white-eyed ♀ gave white-eyed ♂ and red-eyed ♀, although we shall see that there are exceptions to this rule This may be represented diagramatically (Fig 32)

The ♀ transmits the red-eye character equally to both sexes The ♂ transmits the red eye to *one* sex only—the ♀, and fails to do so to the ♂ Hence there must be differences in the sperms, some determining femaleness and transmitting red eyes, the others determining maleness and transmitting white eyes

It might perhaps be put in this way, that the red eye character in the male is associated only with the sperms of low male grade, so that, if it is

absent in the female, it will appear only in the female-developing zygote

In man the study of the sex limited inheritance of certain abnormal conditions points to there

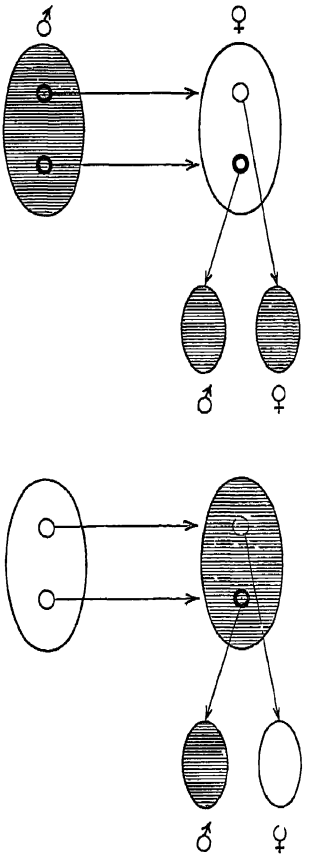


Fig 31 —Diagram (above) of the result of crossing female *Abraxas lacticolor* with male of *Abraxas grossulariata*, (below) of the result of crossing female *A grossulariata* with male *A lacticolor*

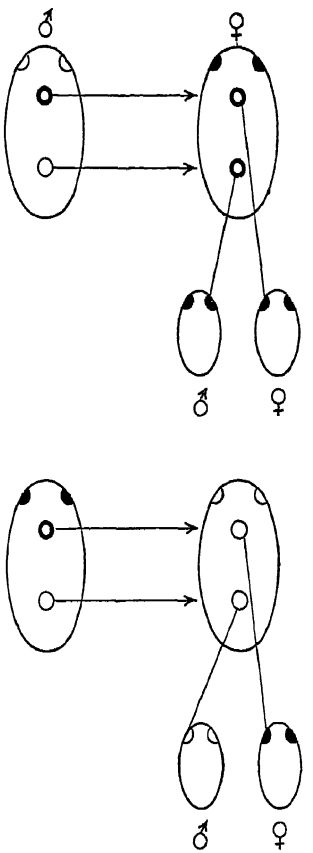


Fig 32 —Diagram (above) of the result of crossing red eyed female *Drosophila* with white eyed male, and (below) of the result of crossing white eyed female with red eyed male

being different grades or kinds of sperms Perhaps the most striking example is *Haemophilia*, a condition characterised by free haemorrhage from even very slight wounds

This condition—a disease or defect of the soma—appears to be capable of manifesting itself only in connexion with the metabolism of the male If an affected man be mated to a normal woman, although the disease does not manifest itself in either the male or female offspring, the male progeny of the daughters, when mated with normal men, tend to show the disease

The subjoined pedigree of a family of haemophilics shows this, but it also shows that the law is not absolute, for 28 in the fourth generation apparently had it transmitted to him by his father 20, unless, indeed, his mother 19 came of a haemophilic stock

The abnormal condition is thus usually not directly transmitted to the male, but is transmitted in a latent form to the female—latent because it does not generally manifest itself in connexion with the female metabolism, and she may transmit it to her male offspring There must therefore be differences in the sperms, some determining and transmitting the disease, others not transmitting the disease

This so-called law of sex-limited inheritance is by no means hard and fast, and many exceptions are found to occur. On the kinetic view of inheritance, that the line of development is merely a line of chemical change readily modified by external conditions, implying the existence of quantitative rather than qualitative

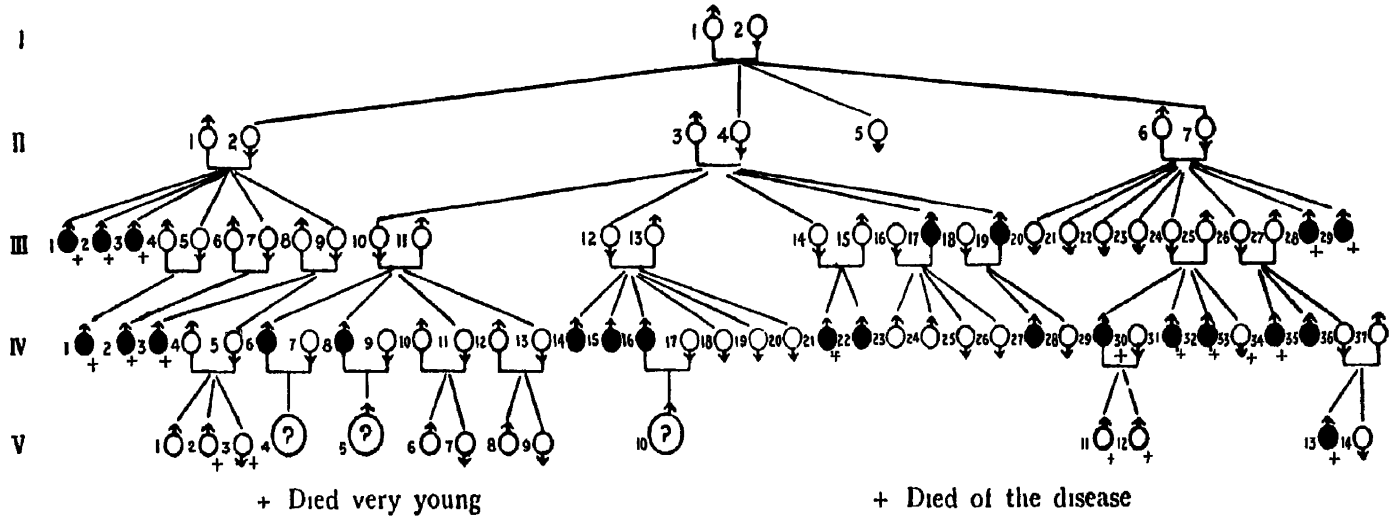


FIG 33 —Pedigree of Haemophilia (Reproduced by permission of Prof K Pearson and Dr W Bulloch from *The Treasury of Human Inheritance* vol 1 Plate XXXVI, Fig 407, issued by the Francis Galton Laboratory of National Eugenics)

difference in the gametes, this is what would be expected

But while these exceptions are readily explicable on the kinetic view they are more difficult to explain on the theory that some *material* in the gametic cells is the determining factor

If there are two *kinds* of eggs or two *kinds* of sperms, by the law of probabilities the number of males and females produced should be equal

This is not by any means always the case In man, for instance, at birth males are to females in Scandinavia as 108 5 to 100, in England 103 6 to 100 But when aborted embryos are examined the proportion is 160 to 100[1] Apparently the number of male conceptions must greatly exceed female conceptions Since in man the evidence is that the differences are in the sperms and not in the ova, it might be maintained that the male-producing sperms are more active or more viable than the female-producing This, of course, is a mere hypothesis It would appear that the mortality is higher in male embryos than in female This view has been supported by King[2] and by Parker,[3] although recently MacDowell and Lord[4] have been unable to confirm it

It must be recognised that there is considerable morphological evidence for the existence of two

[1] Goldschmidt, p 253 [2] *Anat Records*, 1921, 201, 321

[3] *Proc R S* 1923, xcv 551

[4] *Proc Soc Exp Biol and Med* 1924, 22, 389.

kinds of sperms and some evidence for the existence of two kinds of eggs, characterised by differences in the number of chromosomes The differentiation of sperms histologically by the distribution of their chromosomes has proved much easier than the differentiation of ova, and apparently very definite results have been obtained showing differences between sperms which will produce males and those which will produce females But it must be remembered that out of the myriads of sperms produced only a few can be observed, a very small sample can be dealt with, and the question arises is it an adequate and fairly representative sample? In what proportion of the samples examined is the clear cut differentiation of chromosomes demonstrable?

The perusal of many of the papers upon these sex chromosomes, *e g* that of Frolowa[1] on the chromosomes of *Ascaris megalocephala*, shows the difficulties in interpreting appearances and distinguishing actual chromosomes from mere pieces of chromatin

While M'Clung first demonstrated the differences between different sperms, extensive work has been done upon the fruit fly (*Drosophila*) In it the sperms examined before maturation contain, in addition to the usual pairs, two dissimilar chromosomes X and Y, one of which is described as going into one sperm the other into the other.

[1] *Arch Zellforsch* 1913, IX

Zygotes in which one type are found after syngamy appear to develop into females, those in which the other is found apparently into males

In the Aphids and in many other insects there is an unpaired chromosome in the sperm, and when the maturation process occurs it is said to pass into one of the cells, so that the other is devoid of it Here again two kinds of sperms are produced, the former of which will produce a female the latter a male

The evidence of whether in man the so-called sex chromosomes are unpaired or of the XY type is conflicting In fact, the whole question of the numbers of chromosomes is in dispute

The evidence of a morphological distinction between different eggs is less complete In the ruby tiger moth a pair of unequal chromosomes, one going to one ovum the other to the other in maturation has been described by Seiler, and in some strains of the currant moth Doncaster found ova with one chromosome missing, *i e* an unequal number of chromosomes

It is perhaps only natural that students of genetics and cytologists should have arrived at the intrepretation that the difference in sex is *caused* by the differences in the chromosomes But, again to cite Doncaster's illustration, it would be as reasonable to argue that a stag's antlers are the cause and not merely a characteristic of his sex As already argued, the development of such defi-

nite structure is probably not without significance, and the dose of chromatin developed as the result of the metabolism of the cells may act as a stabiliser of the line of metabolism rather than as a determinant of it All the germs of one grade of potency may develop one arrangement, those of a different grade another arrangement

The extraordinary irregularity in the chromatin distribution in animals closely allied, the existence of sperms with no sex chromosomes, of others with a 'X' chromosome only, of sperms with 'Y' chromosome, of sperms with equal chromosomes, of ova with equal chromosomes and of ova with dissimilar chromosomes all seem to indicate that the chromosome distribution is secondary to some more fundamental character, that it is rather an expression of a line of metabolism than a determining factor

The association of somal with gametic characters in the sexes has been explained on the Mendelian theory of linked characters, and this has led to the conclusion that the sex chromosomes carry the determinants of certain somal characters, that they are therefore more than mere sex determinants Thus, in the accompanying diagram, based on Morgan's work on the fruit fly (*Drosophila*), the results of mating a red-eyed female with a white-eyed male are shown in F_1 and F_2 generations (Fig 34)

It is assumed that certain sex chromosomes carry the determinants for red eyes and that others

carry those for absence of the pigment, that the former is dominant to the latter, and that the white-eyed male has two kinds of sperms, one with

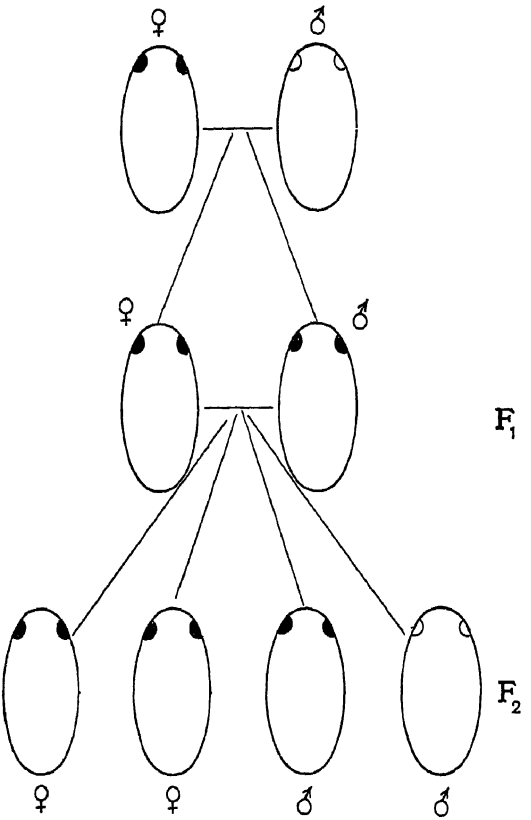


FIG 34.—To show the result of mating a red eyed female *Drosophila* with a white eyed male and interbreeding in F_1 generation

X and one with Y sex chromosomes, both without the pigment factor (Fig 35)

The figure and description implies that in the F_1 generation the sex chromosomes in both sexes are of two kinds—one red and one white determining, that in fact in crossed races of *Drosophila*

the law of two kinds of sperms and one kind of egg does not hold

The experimental result was that in the next generation there were red-eyed females, red-eyed

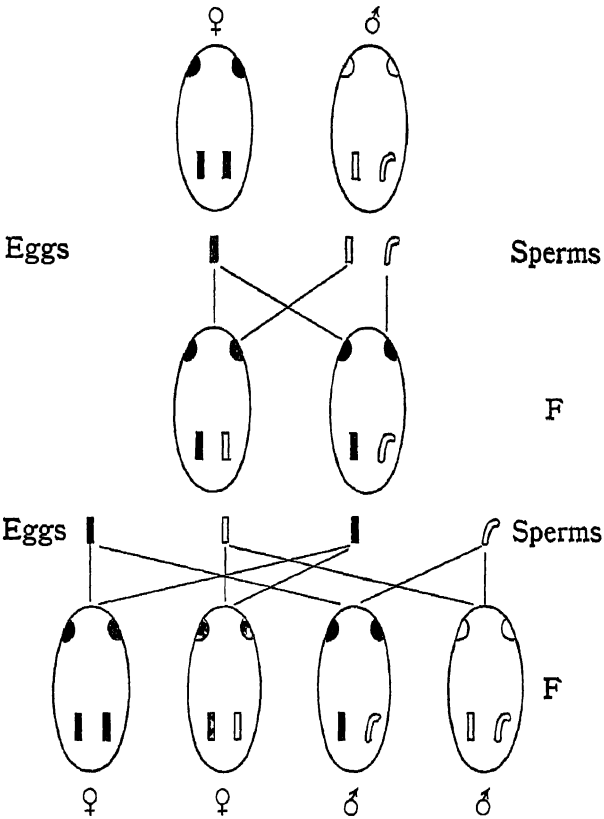


FIG 35.—Diagram to show explanation of the result shown in Fig 34 on the chromosome theory

males and white-eyed males—no white-eyed females

It is as easy to explain these results on the view that the sperms with the Y chromosome have a metabolism more markedly in the direction of maleness than those with the X chromosome

All the progeny from the former should be male, from the latter female The dominant influence of metabolism in the zygote towards red eyes will secure that all the progeny are red-eyed

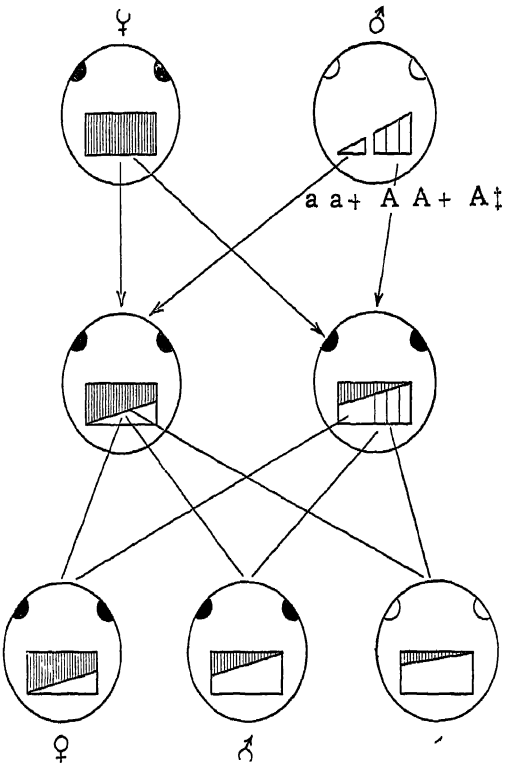


FIG 36.—Diagram to show how the result shown in Fig 34 may be explained on the theory of there being quantitative differences in the male gametes The degree of "maleness" is indicated by a a+ A A+ A‡

In the next generation the sperms of greatest maleness may completely dominate the diluted tendency to red eyes in the ova fertilized by them, while those of lower maleness may be sufficiently powerful to determine the formation of a male but not sufficiently potent to overcome the tendency to red eyes (Fig 36)

Thus, mere *quantitative* differences appear to be sufficient without postulating the development of two *kinds* of sperms

It will be objected that on this theory of quantitative difference there should be functionally intermediate forms of ova or sperms But the argument seems hardly valid since, as already indicated, the grading is not necessarily gradual but may be abrupt (Fig 9 p 37)

It will be shown later that there is good evidence of various degrees of maleness in the sperm of certain insects (p 104)

In the investigations on *Drosophila* certain unexpected forms not apparently explicable on the chromosome theory have been found to occur, and great ingenuity has been shown in explaining them in terms of this theory Thus, a red-eyed male mated to a white-eyed female usually gives red-eyed females and white-eyed males But sometimes white-eyed females and red-eyed males occur

This has been explained by Bridges on the ingenious hypothesis that the X chromosomes of the egg do not separate (non-disjunction) but that both remain in the ovum or are passed out into the polar body In support of this view he cites an observation by Wilson on the sperms of *Metapodius* Wilson found three spermatocytes in which X followed Y to one pole at the reduction division [1] By non-disjunction two kinds of eggs might be

[1] *Genetics*, 1916, 1, p 11

produced, while as we know there are two kinds of sperms . Fig 37 shows the explanation that is given, and brings out the point that it is assumed

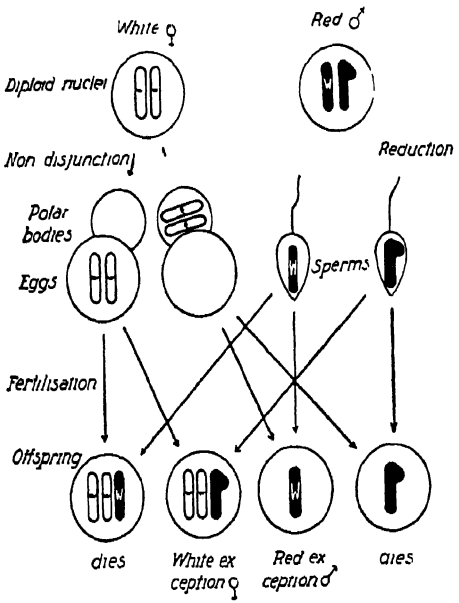


Fig 37 —Explanation of an exceptional result of crossing white eyed female *Drosophila* with red-eyed male by the non disjunction of the chromosomes leading to there being two kinds of eggs (Goldschmidt, after Bridges)

that two of the four zygotes represented in the third line die

If these two assumptions are made, the explanation is easy, without them, the theory that the chromosomes are the determinants breaks down

A consideration of the progeny of the exceptional white-eyed female with a wild male shows that there are eight possible results, of which six have been found It is assumed that the two which have not been found die

What is considered the clinching argument for the material basis of sex inheritance is the fact that the ova of the exceptional white-eyed female has been found to have the odd Y chromosome and two X chromosomes This certainly shows a close correlation of chromosome distribution and the course of development, but it cannot be said, as Goldschmidt says of it, that "The evidence stands on the same level as a demonstration in experimental physics" Nor can we accept his conclusion (p 73) that "The mechanism for the normal distribution of the sexes is thus completely explained" He himself in the later parts of his book shows that this is not the case, and that other factors besides chromosome distribution play an important part.

It would of course be extremely curious if the line of development of the somal cells was dissociated from that of the germ cells, if the germ cell of a red-eyed female did not tend to produce red-eyed females or the sperm of a white-eyed male did not tend to impose the character of white eyes upon the egg it fertilised—the result depending upon the dominance of one of the conjugating gametes It seems manifest that if two chromosomes instead of one are shed from the cell *with the accompanying protoplasm and centrosome* a totally different complex is left, and that the one cannot be expected to develop on the same lines as the other If this be so, it seems unnecessary to

postulate that the result is due to the loss of the directional influence of the chromosome

So far sex determination in the Metazoa has been considered As regards the Protozoa, Clifford Dobell[1] has shown that in the reproduction of *Aggregata Eberthi*, a parasitic protozoa of the Sporozoa Group, in which sexual reproduction occurs in the cuttle-fish as host and asexual reproduction in a crab, the chromosomes are the same in number and character throughout the various forms which the cell assumes and that there is no difference in the numbers between the male cells and the female cells. He also considers the process in other Sporozoa and in other Protozoa, and he contrasts these with the process of gametogenesis in the Metazoa In the light of these investigations he argues against the conclusion that chromosomes are determining factors in heredity and in sex determination

On the chromosome theory of sex determination the lability of sex is most difficult to understand On the theory that the chromosome dose acts as a stabiliser it is more easy In certain species the stabilisation is prepotent, in others it is less marked, and in some it seems to be almost non-existent, and the experiments of Meisenheimer seem to show that in insects the determination of sex before or at fertilization is specially well marked He found that the removal of the sex gonads in the pupa

[1] *La Cellule*, 1924, 35, 169

state of some lepidoptera does not modify the development of the sexual characters of the imago It must be remembered that it is upon insects that most of the work upon chromosomes has been done.

That the sex into which the egg will develop and the distribution of chromosomes may be altered by external conditions is indicated by the observations on the Psychid, *Talaeporia tubulosa*, where two kinds of eggs are produced When a female is to be produced the X chromosome goes into the polar body, when a male is to be produced it remains in the egg, and Seiler, by counting the chromosomes, found that the numbers of cases of these two conditions corresponded with the proportion of sexes produced Further, it was found possible to modify the sex proportion and the chromosome distribution by varying the temperature

	Polar	Not in Polar	♀	♂
At 3–5° C	48	31	155	100
35–37° C	52	84	62	100

This seems a clear indication that the distribution of chromosomes is determined by the metabolism of the protoplasm and, if this be so, why should the resulting sex not also be determined by metabolism ?

Banta and Brown[1] describe an interesting case of sex determination by environmental conditions In the *Cladocera* parthenogenesis goes on for long

[1] *Proc Soc Exp Biol and Med* 1924, 22, 77

periods, females being produced Sometimes males arise from eggs indistinguishable from the others At times sexual eggs appear which, when fertilized, undergo early developmental stages and then enter a latent period which may last for months or years After dessication or freezing they develop in water into females

Experiments upon *Moina macrocopa* showed that crowding was followed by variable production of males and that the addition of CO_2, uric acid, etc, tends to increase their production The period during which these changes could be induced was from two to four hours before the eggs leave the ovary at which time maturation by single division without reduction occurs The authors conclude "The presumption is strong that environmental conditions, in some manner, alter the chromatic behaviour in the single maturation division and thus affect the sex" Unfortunately for the conclusion, in the next sentence they confess that Miss Taylor has shown that the female and male producing eggs have the same number of chromosomes They conclude that production of male eggs is associated with a lower metabolic rate in the mother

Hertwig found that he could vary the proportion of sexes in the frog by keeping the fertilized eggs at different temperatures Those kept between 15 and 18° C gave 260 ♂ and 85 ♀ Those at 30° C gave 344 ♂ and 319 ♀

He also found that when the eggs were immediately fertilized the proportion of the sexes was about the same, but when they were kept some time before fertilization the proportion of males to females was as much as 700 to 100 Kuschakewitsch, after longer intervals, got all the eggs developing into males

It may be urged by the champions of the theory that sex is always determined through the chromosomes, that keeping the eggs may have so modified the distribution of the chromosomes as in this way to alter the sex of the animal into which they will develop Eidmann[1] states that overripe eggs show a retrogression of a chromosomes, surely an expression of alteration in metabolism

If chromosomes are the determining factor the characters developed should be clear cut and distinct, there should be either maleness or femaleness But, as we have seen, intersexual forms occur not infrequently, and it has tried the ingenuity of the champions of the material basis of sex determination to explain them On the other hand, if we accept the view that the distribution of the chromatin is merely an index of the metabolism of the gamete and that it is the *line of metabolism* which determines its future, and that the chemical changes constituting the metabolism are easily modified by external conditions, then the occurrence of all varieties of intersexual

[1] *Biol Ztsch* 1922, 42, 97

condition becomes intelligible, and this view still allows us to regard the chromosomes as stabilisers of the line of development

Thus, any alteration in the potency of the maleness or femaleness of the gametes, as figured in Fig 36, might lead to a disturbance in the proportion of sexes produced, or even to the development of intersexual forms neither true males nor true females

That it is necessary to postulate *quantitative* variations in the element of maleness is shown by the investigations of Goldschmidt, one of the great champions of the prime part played by chromosomes in the determination of sex He found that certain strains of the gypsy moth *Lymantria* produce sperms possessing a great tendency to maleness, and that these males when mated with a female gave a high proportion of males and, in addition, females with certain somal characters of the male, *i e* intersexual forms He made the further interesting observation that the last somal organs to develop in the pupa are those which most readily show the change of sex characters, and that the gonad is the organ which resists most strongly the influences towards sex reversal

These intersexual forms must be explained by grades of potency in the sperms, and do not indicate the existence of different kinds of egg

In all probability the observation of Hertwig that frogs' eggs fertilized by the sperm of certain males

give a different sex ratio to those fertilized by the sperm of other males may be explained in the same way He also found that in certain districts the young frogs developed in an indifferent form, neither male nor female, and this seems to support the metabolic or kinetic view

But in the production of intersexual forms other factors undoubtedly may play a part, and these must be considered when the influence of the gonads upon the soma is dealt with (p 121)

The cases of sex reversal already considered seem to indicate that the early determination of sex, associated with, but not necessarily dependent on, the special distribution of chromosomes, is not definitive, but that it is more of the nature of an impulse given in a certain direction, an impulse which may be sufficient to carry out complete development along a definite line or which may be over-ridden by subsequent changes

To summarize There is evidence to show that the sex of the offspring may be in part at least determined (1) before fertilization where there are either two distinct kinds of eggs, or eggs of graded differences, or (2) at the time of fertilization where there are two kinds or different grades of sperms

There is also abundant evidence that this determination may be over-ridden by other conditions operating before or after fertilization The case of *Bonellia* is perhaps the most striking instance of this, and it is further illustrated by the investi-

gations of Hertwig on the effects of the condition of the eggs of the frog at the time of impregnation upon the proportion of sexes produced

Since the above was written a masterly criticism of the usually accepted theories of heredity and sex determination has been published by Fick of Berlin [1] I append a translation of the admirable abstract published in the *Berichte u d ges Physiol* 1925, 30, 223 "The author examines some 'dogmas, almost universally accepted to-day, in the province of the theory of heredity,' with regard to their correctness from a general biological standpoint, and after unprejudiced investigation of the facts reaches the following conclusions (1) The theory of maintenance of the individuality of the chromosomes is a hypothesis which cannot stand against critical consideration (2) The nucleus, the chromosomes or the chromatin, cannot be the bearers of heredity, the chromosomes, as 'important organs of activity of the cells,' will, it is true, have to play an important part in the 'carrying out of heredity,' but probably the whole cell takes part in the transmission of the collective properties of an organism (3) The transmission-substance is the individual plasma By this the author understands 'not a combination of different organic substances flung together by chance, but a quite definite chemico-physical

[1] "Abhandl d preuss Akad d Wiss" (*Phys. math kl* Jahrgang 1924, No 3, pp 3-34)

system' In the germ-cell a characteristic is not represented by an independent particle, but the characteristic originates first of all as the terminal member of a series of reactions of a chemico-physical nature, this series of reactions being necessitated by the plasma of the sex cells (4) The theory that the paternal and maternal loops remain apart after fertilization (Gonomery) is shown to be quite untenable (5) It is highly improbable that the conjugating chromosome-halves consist of one part definitely coming from the father and one from the mother (6) Sex difference is not to be regarded in the same light as some or other characteristic differences Sex chromosomes are not determinative of sex, but at most are a peculiarity of sex The theory of progametic or syngamous sex determination has little probability (7) Up till now it has not been proved that Mendelism and the 'manoeuvring of the germ loops' have anything to do with one another Mendelism can quite well be combined with the chemical concept of heredity (8) Suppositions as to crossing over, as well as 'cross exchange' itself, have in themselves something quite improbable Especially remarkable are the facts that this exchange is said to take place only in one sex (in *Drosophila* only during maturation of the ovum), and that the Y chromosome, though it represents a regular chromosome, is said to have no importance for heredity Such and similar considerations cause the author

to assume that Morgan and his school, in spite of noteworthy deeds, have not yet found the right way to clearing up the question of heredity (9) Heritability of acquired characteristics is to be accepted Changes in the germ plasm may arise gradually thereby, but do not become operative till past a certain threshold (corresponding to the gradual building up of a chemical substance) "

The student should read

1 Doncaster's *The Determination of Sex* Cambridge University Press 1914

2 Goldschmidt's *The Mechanism and Physiology of Sex Determination,* translated by W J Dakin Methuen & Co , Ltd 1923

The evidence so far examined thus seems to indicate that

1 In many protozoa and in all metazoa a somal part is developed from the germ cells in each generation

2. In metazoa reproduction primarily consists in the throwing off of germ cells to undergo division and to produce another generation (parthenogenesis)

3 The division of the germ cells may be accelerated or retarded by various conditions, *e g* chemical changes Conjugation of these cells is one of the accelerating factors

4 The transition from parthenogenesis to sexual reproduction seems to depend upon imperfect nutri-

tion, leading to the development of individuals either producing ova incapable of developing without fertilization or producing germ cells altogether incapable of developing but capable of acting as fertilizers—the sperms

5 When sexual reproduction is established some germ cells tend to be large and to contain stored nutrient material (the ova), while others are small (the sperma) (In some infusoria conjugation takes place between a large and a small individual)

6 Originally the two kinds of germ cells were produced in a single individual (hermaphroditism or monoecism) (cestodes, oligochaetes, trematodes)

7 The production of one or other kind of gamete probably became more predominant in the same individual at certain times (crustacea, hagfish, etc)

8 Finally, in each individual one kind of gamete, sperm or ovum, alone developed, and males and females were thus differentiated

9 The character of the gamete produced seems to have been first determined by the environment of the individual (barnacles, bonellia)

10 The gametes of each sex by the law of hereditary inertia tend to develop into the sex of its producer, and hence in every zygote there is a struggle between development into male or female

11 The line of development which will be followed may be determined by external or somatic

conditions (bonellia, barnacles, frogs), or by the potency of the influences of one or other of the conjugated gametes (gypsy moth, frog)

12 The differences in potency may be most marked in the ova (birds, currant moths), or in the sperms (mammals, fruit fly, etc), and these differences may become so distinct that it is possible to speak of male-determining and female-determining ova or sperms

13 In many species the difference of potency appears to be correlated with differences in the distribution of the chromosomes of the gametes

14 In the gamete which varies in potency an asymmetry in the distribution of chromatin has sometimes been observed

15 The asymmetry may consist in either (*a*) the presence or absence of a particular unpaired chromosome, or (*b*) the presence of an asymmetric pair of chromosomes (X and Y)

16 The chromosome arrangement may be merely the morphological expression of a particular line of metabolism, and it may act as a stabiliser of a line of metabolism in the zygote, or it may be the determinant of the line of development towards male or female So far the evidence does not establish that the correlation between chromosome distribution and sex determination is causal

17 While the sex into which the germ cells will develop depends upon the condition of nutrition

of the soma or upon other external conditions, or upon the relative potency of the conjugating gametes, the sex characters of the body or soma depend upon some other factors acting while it develops

18. Primarily the soma is equipotential as regards its sexual development In most animals it is fundamentally neuter

CHAPTER V

RELATIONSHIP OF GERM CELLS TO SOMAL CELLS, AND TO THE DEVELOPMENT OF THE GONADS

As already indicated the somal cells are simply thrown off from the zygote to nourish and protect the germ cells But the separation of the two

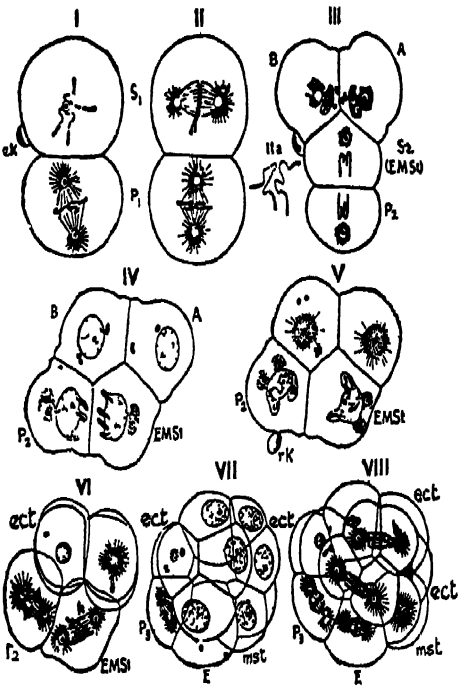


FIG 38.—The early divisions of the zygote of *Ascaris* to show the separation of the primary germ and primary somal cells in the first cell division (Boveri)

types of cell from one another is not always discernable till somal development has gone on for some time

In *Ascaris* the differentiation takes place at the first division of the zygote, and the gametic cell retains its two typical chromosomes, while the other, the first somal cell, before division shows a breaking up and loss of chromatin The gametic cell undergoes three more similar divisions (Fig 38), so that in the sixteen cell stage of

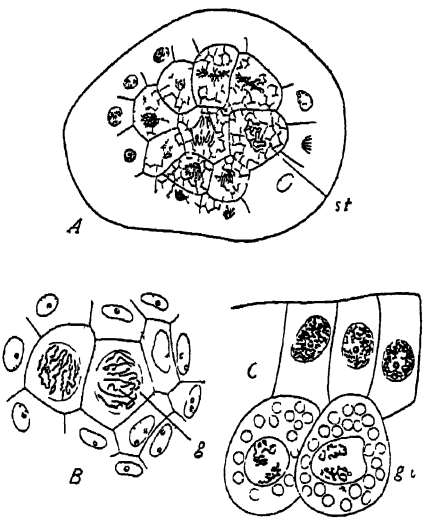


Fig 39 —The appearance of germ cells among the somal cells in *Cyclops* g the germ cells (Hacker)

the morula there is one gametic cell and fifteen somal cells

In other invertebrates the differentiation is not detectable at so early a stage, but the cells which are the progenitors of the gametes gradually stand out from the surrounding somal cells of the ectoderm and endoderm by enlarging and taking special characters In *Cyclops* this differentiation occurs in the morula stage (Fig 39)

The germ cells are therefore not to be considered as special products of any layer of the embryo, and they cannot be spoken of as of epithelial or of mesenchymatous origin

The early distinction between the germ cells and the somal cells in vertebrates is clearly indicated by the investigations of F A Woods "On the

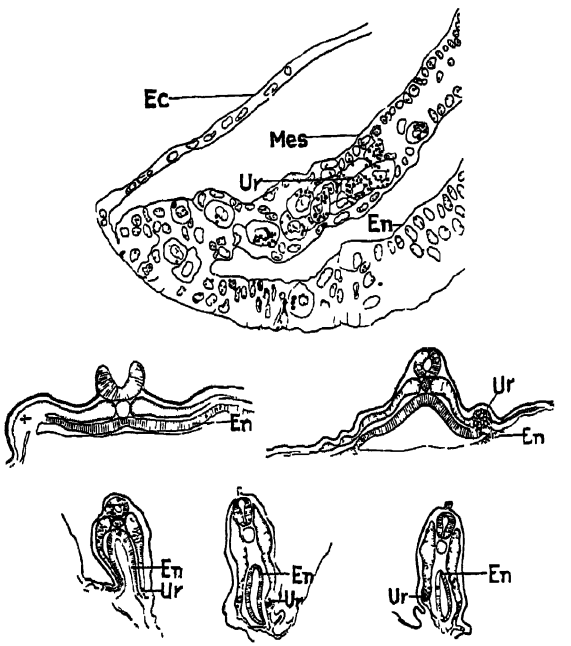


Fig 40 —Passage of germ cells, *Ur*, inwards from yolk sac at the edge of the blastoderm to the genital ridge in *Acanthias* The small figures show the passage of the germ cells The large figure is more highly magnified to show the characters of the germ cells, *Ur* (Woods)

Origin of the Germ Cells in Acanthias"[1] He showed that they may be first seen in the yolk sac at the edge of the blastoderm, and that they move, or get displaced from there to the substance of the mesoderm and so to the genital ridge (Fig 40)

[1] *Am J of Anat* 1901-02, vol 1 p 307

In the fowl Defretin[1] describes the gonocytes as appearing first in the mesenchyme

In higher vertebrates the germ cells are at first indistinguishable from the cells covering the lining membrane of the body cavity or coelome It is over the genital ridge that the differentiation becomes manifest The cells enlarge and penetrate into the subjacent tissue These enlarged cells are said to be recognisable in the human embryo of about twenty days

While the complete independence of germ cells and somal cells is very generally accepted, and is in fact the first article of Weismannian faith, the possibility that the somal cells originally thrown off from the gametes may be capable of again reverting to gametic cells must be considered The question is manifestly one of enormous importance since it bears so directly on the transmission of characters through the germ cells alone

In some invertebrates the evidence points strongly in this direction Hargitt[2] states that in *Campanularia* (Cœlenterata) the basal part of an endodermal cell may form an egg and the distal part remain functional epithelium In the oligochete *Criodrilus*, Janda found that, on cutting off anterior segments, new gonads were formed from the peritoneal epithelium of the septa Kammerer states that in the ascidian *Ciona intestinalis* removal of the lower part of the body with the

[1] *C R Soc Biol* 1924, 91, 1082 [2] *J of Morph* 1913, 24, 383

hermaphrodite gonad is followed by a regeneration both of the body and of the gonad, manifestly from somal cells or from germ cells lying dormant in the body Hargitt [1] found that the germ cells of the *Diemycytelus viridescens*, an amphibian, may be formed from peritoneal epithelium

The study of cases of sex inversion in vertebrates, from female to male, certainly seems to show that cells at first indistinguishable from the mesenchymal cells of the peritoneum on the gonad may become spermatogonia Such cases have been described in the fowl by Miss Fell[2] and by Gatenby [3]

In mammalia the cells which first grow down into the genital ridge become what may be called the **inter-renal tissue** which in higher vertebrates forms the cortex suprarenalis These structures are distinguishable about the third week of foetal life in the human subject In the middle of the second month of gestation, about the sixth week, the male **gonad** can be recognised, but the female is not yet differentiated and the sex can be determined only by exclusion (Kennard) [4]

The downgrowing cells of the gonads are characterised by an abundance of lipoids in their protoplasm They come to be differentiated into two sets

1 The true germ cells 2 Ancillary cells

[1] *J of Morph* 1924, 39, 63 [2] *Brit J of Exp Biol* 1923 1 97
[3] *J Mic Sc* 1924, 641
[4] *Med J.* 1922, 39, 96, abstracted in *Berichte u d Physiol* 1923, 20, 339

Ovary. In the ovary groups of cells get cut off from the down growths, and one of each group enlarges and forms the true ovum, while the others

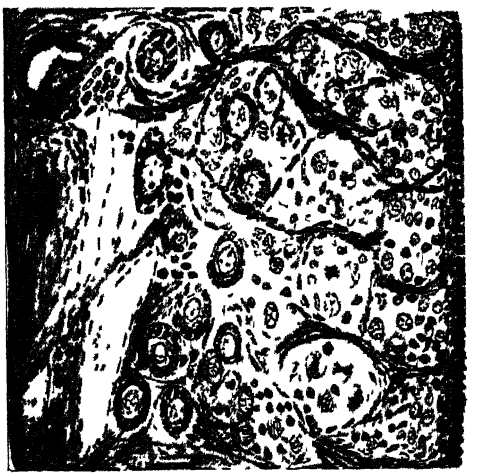


FIG 41.—The development of the Graafian follicles and interstitial cells of the ovary (Louise M'Ilroy)

arrange themselves round about it as ancillary cells to form the zona granulosa and the theca interna Together they constitute a Graafian follicle (Fig 41)

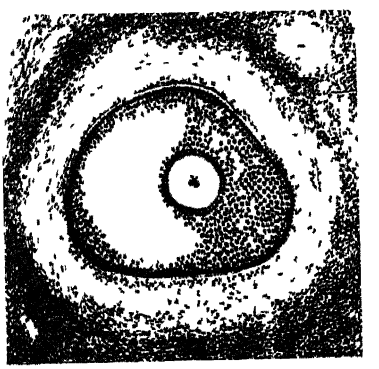


FIG 42.—A Graafian follicle with fully developed zona granulosa enclosing the ovum and with liquor folliculi appearing among the cells (Settheim)

As the ovum grows the cells of the zona granulosa multiply and fluid appears between them, so

that finally the follicle is lined by several layers of cells to which are attached by a strand of cells—the discuss proligerus—a layer of cells which surrounds the ovum (Fig 42).

Between these Graafian follicles, in some animals at least, a number of the ingoing cells are left as interstitial cells (Fig 43) In man and in some other animals these may possibly be derived from the cells of the follicles

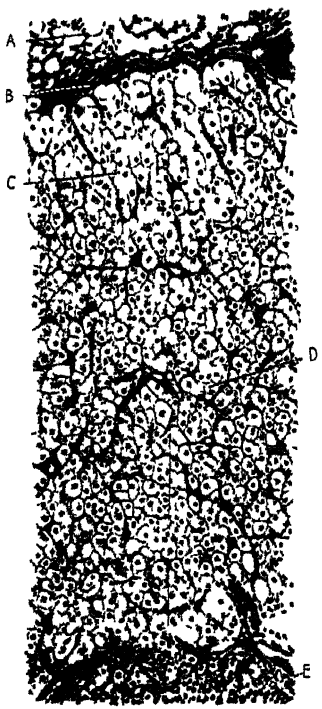


Fig 43 —Interstitial cells from the ovary of the rabbit (Biedl)

When the follicle is fully formed it bulges on the surface of the ovary and finally bursts, discharging the ovum into the peritoneal cavity Its future history is considered on p 180

But all the follicles do not ripen In a considerable number the ovum ceases to develop and degenerates, and the follicle collapses, leaving a mass of cells of the zona granulosa and the theca interna which may escape into the surrounding tissue to form interstitial cells (Fig 44)

These ancillary cells, like the cells of the inter-

renal bodies, are loaded with lipoids, but in the Graafian follicles the ovum during its growth seems to draw off the supply from the cells of the zona granulosa

When the ovum of a ripe follicle is shed, an increase in the size of the ancillary cells of the follicle takes place to form the corpus luteum, and

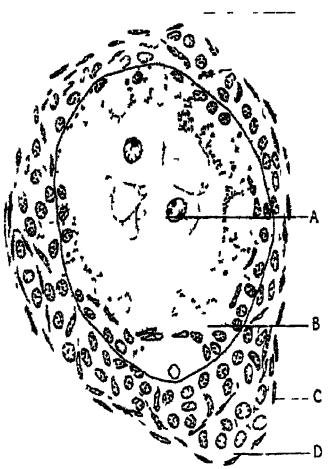


FIG 44 —Atresic Graafian follicle. (After Limon)

these cells are now loaded with lipoids The further history and physiology of these will be considered on p 180

Testis. In the testis the down growths of cells become tubular to form the seminal tubes Certain of the cells (spermatogonia) undergo development into the sperms

Among these spermatogonia are other cells which increase in size, become loaded with lipoids, and form the cells of Sertoli

Between the tubules are epithelial-like cells also loaded with lipoids, known as the interstitial cells or cells of Leydig Some observers consider that they are derived from the mesothelium, while others describe them as developed from the fibrous tissue cells of the inter-tubular tissue As already indicated, their source is probably similar to that of the germ cells and, whatever changes they may undergo or whatever type of cell they may resemble, they should be considered as of a different stock than the ordinary tissue cells

Developmental, histological, and chemical evidence indicates that the cells of the inter-renals, the cells of the gonads, those developing into ova and sperm, and those forming the ancillary system of cells have a common origin, and that they may all be considered as germ cells The possibility that somal cells may revert to the condition of germ cells cannot be excluded

The way in which the cells of the gonads modify and control the growth and development of the somal cells must next be considered

CHAPTER VI

THE INFLUENCE OF THE GONADS UPON THE SOMA

In previous chapters the sex characters, gonadal and somal, have been considered, and cases of dissociation of these have been referred to A study of the determination of sex has shown that factors other than the mere arrangement of special loops of chromatin play no inconsiderable part, and that the chromosome distribution may be merely a manifestation of a particular line of metabolism

The study of the development of inter-sexual forms indicated that the development of the gonads and of the somal or secondary sex characters may be influenced by something inside the body The possible influence of the gonads upon the development of the soma with its secondary sex characters and upon the physiology of sexual life and on the nutrition of the zygote may now be considered

In the first place there is an interesting parallelism between the development and growth of the body and that of the gonads

INFLUENCE OF THE TESTES UPON THE SOMA

In the human male at the time of birth the testes show tubules filled with cells, some of which



FIG 45 —Testes (human) at birth (Stohr)

are the precursors of the sperms (spermatogonia), some probably nutrient in nature (the cells of Sertoli) Between the tubules the interstitial cells



FIG 46 —Testes of boy of nine years old (Spangaro)

are well developed In connection with their marked development the occurrence of mimicry of

the sexual act soon after birth in some species, *e g* lambs, is of interest (Fig 45) Throughout childhood the testes show very slight growth till about the tenth year (Fig 46)

During this period the interstitial cells present at birth decrease in number Bouin and Ancel have described the disappearance of the foetal

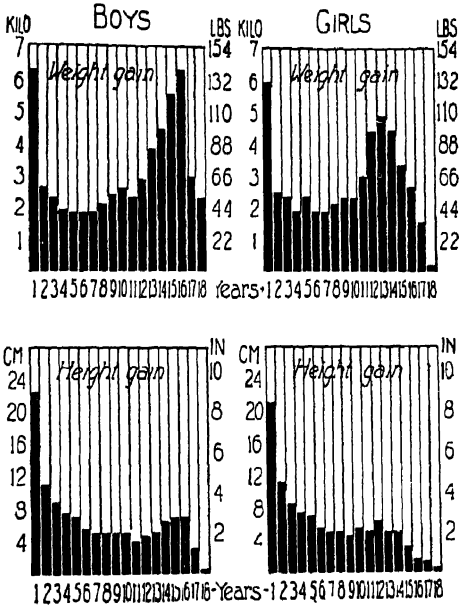


Fig 47 —The annual increase in weight and height of boys and girls (Holt)

interstitial cells in the horse between birth and the tenth month of age, and the appearance in their place of a new type of cell which they call the xanthochrome cells, from the character of their granules As spermatogenesis begins, about the eleventh month, these cells are replaced by a new set which persist throughout life The chief interest in these changes is the similarity of the

disappearance of the foetal testicular cells with the disappearance of the cells of the cortex suprarenalis during the second week of extrauterine life, which will be described later (p 153)

In the human subject the interstitial cells increase just before puberty, but whether they are or are not identical with the cells at birth has not been investigated

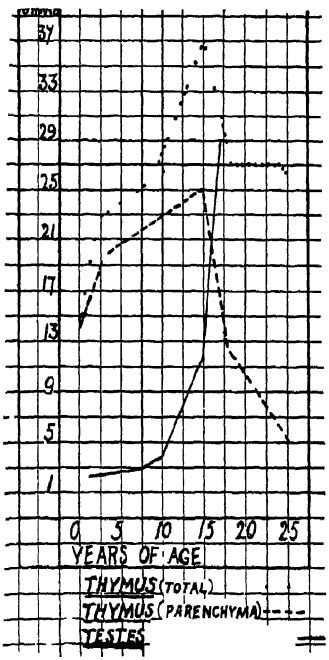


FIG 48.—To show the growth of the testes and of the thymus from birth to puberty

Throughout the prepubertal period the rate of increase in weight of the body may be divided into two periods 1st One of rapid growth from birth to the end of first year 2nd One of slower growth to the twelfth year (Fig 47)

This is followed by a prepubertal increase in the rate of growth, which coincides with the period of commencing rapid growth of the testes The following chart, based upon 185 observations from the post-morten records of various children's hospitals analysed by me shows this (Fig 48)

A chart given by Weil without any indication of its source (Fig. 48A) shows the same relationships

between growth of the body and growth of the testes and thymus

At this period atrophy of the *thymus* has not begun and, if that structure exercises a growth-

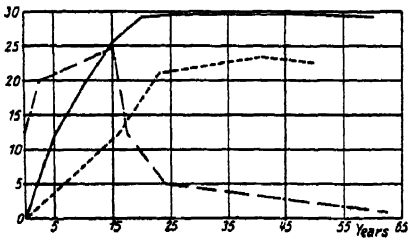


FIG 48A —Relative increase in weight of body and of testes and thymus (Weil)
——Length of body, Weights of—— Thymus, Testes

stimulating action, it may operate along with the testes That these two organs act reciprocally is indicated by my experiments[1] on simultaneous removal of the testes and thymus in guinea pigs

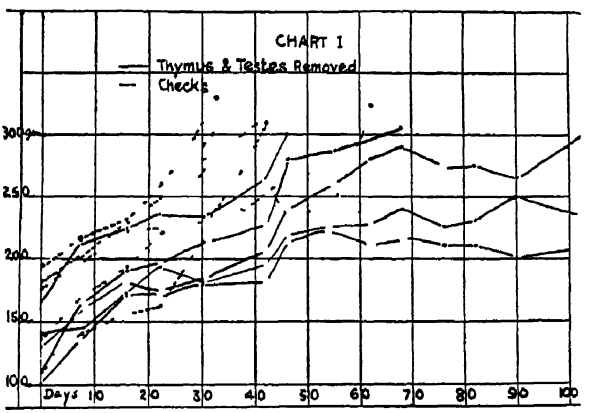


FIG 49 —The rate of growth of young guinea pigs normal, and after removal of thymus and testes

soon after birth This markedly delays growth till the size is reached at which sexual maturity should manifest itself (Fig 49)

[1] Noel Paton, *J of Phys*, 1911, 42, 267

As puberty supervenes it is characterised by a rapid increase in the size of the testes, by a secondary increase in the interstitial cells and by the commencement of spermatogenesis (Fig 50) At the same time the secondary sexual characters become prominent—the increase in the penis, the

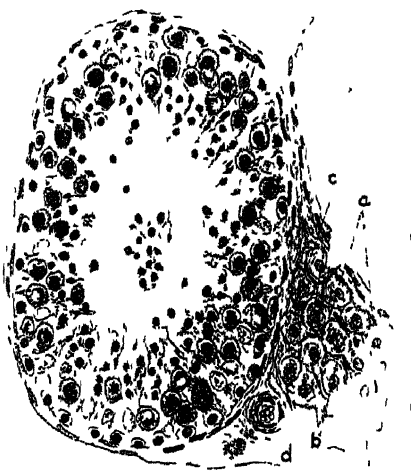


Fig 50—Testes of man of forty eight years old (Spangaro)

growth of pubic hair and the growth of hair on the face The vocal chords lengthen and the voice "cracks" and deepens

The period of the onset of puberty varies greatly, but it occurs most frequently about the fifteenth year

The influence of the testes upon the soma is further demonstrated in several ways

1. **Castration.** That the development of the somal characteristics of the male is largely determined by the development of the testes is proved

by the influence of early castration in the human subject in checking its onset and in leading to a persistence of the infantile type of body. The penis and prostate, the hair on the pubis and face, and the larynx do not grow as they do in the normal male The ossification of the long bones is delayed so that they tend to be long, while the process of periosteal growth in thickness is decreased and the bones tend to be slender There is a tendency to the accumulation of fat under the skin, often on



FIG 51.—Head of cock at time of castration and at intervals after up to 3½ months showing the change developing (Pezard)

the buttocks and breasts, and the temperament is apt to be lethargic

In such animals as the stag, in which the annual onset of sexual activity is preceded by the growth of antlers, castration prevents their development and leads to the formation of nodular masses of bone in their place In hollow horned animals, in which the male is differentiated from the female by these appendages, castration prevents their growth

The marked differences in plumage and other characters between the sexes in some birds, *e g* the common fowl, pheasant and duck, makes them specially suitable for studying the effects of

castration Removal of the testes prevents the development of the characteristic secondary characters of the male, and, if these have developed, leads to the retrogression of some of them, such as the comb and wattles of the cock (Fig 51)

2. Eunuchoidism. Cases not infrequently occur in which neither the testes nor the secondary



Fig 52.—Man of 51, showing eunuchoid condition (Tandler and Grosz)

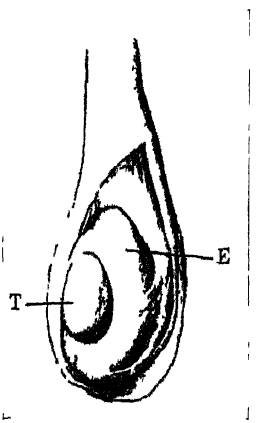


Fig 53.—Testes, *T*, and Epididymis, *E*, from eunuchoid man

sexual characters develop (Fig 52 and 53) This has been called the *Eunuchoid* condition, and, in the light of the effects of castration, it is generally ascribed to a primary failure in the growth of the testes But it must be remembered that it is possible that both the gonadal and the somal changes may be due to some common factor

Thus in non-development of the thyreoid gland the same persistence of infantile characters in

gonads and the soma are observed, while probably defective growth of the anterior lobe of the pituitary may be accompanied by similar failures in development It is possible that both of these conditions may act upon the body through the gonads, but upon this we have no evidence except perhaps that in cretinism, due to a-thyreoidism, there is an arrest of the growth of the cartilaginous bones in length which is not observed in the eunuch or in the eunuchoid state This at least points to the action of the thyreoid being a direct one upon the gonads on the one hand and the soma on the other

3 Pubertas Praecox. The evidence afforded by premature sexual development (pubertas praecox), where both gonads and soma attain maturity at an abnormally early age, is generally accepted as an indication of the influence of the testes upon the body, and the records of some of the cases support the view

A case described by Sachi and quoted by Biedl is of interest A boy, who until five-and-a-half years old appeared quite normal, gradually developed a strong growth of bone and powerful development of muscles Pubic hair appeared, and a beard grew The left testicle was greatly enlarged At nine-and-a-half he measured 143 cm and weighed 44 kg The left testis was removed, and showed the characters of an alveolar carcinoma the physical development retrogressed and the boy became more normal for his age.

The condition of pubertas praecox is also associated with hypertrophy of the inter-renal tissue of the cortex suprarenalis (p 156), and more problematically with irritative changes in the anterior lobe of the pituitary (p 166)

4. Transplantation. The influence of the testes on the development of the secondary sexual characters was long ago demonstrated by Berthold of Gottingen In 1849 he showed that a cockerel which



FIG 54 —To show the effect of transplanting the testes of a guinea pig into a castrate female From left to right masculine female, castrated female, normal female, normal male (Steinach)

had been castrated, and which would have grown into a capon without the development of the comb, wattles and other male characters, did develop all the characters of the sexually perfect cock if a piece of the testes were grafted

This observation of Berthold has been amply confirmed by a large number of subsequent investigators, not only on fowls but upon amphibia and on mammals Nussbaum showed that the characteristic development of the clasping pads on the thumb of the male frog in the breeding season did not develop after castration and that the

sexual act of the "clasping reflex" was not performed If a testicular graft were made the pads

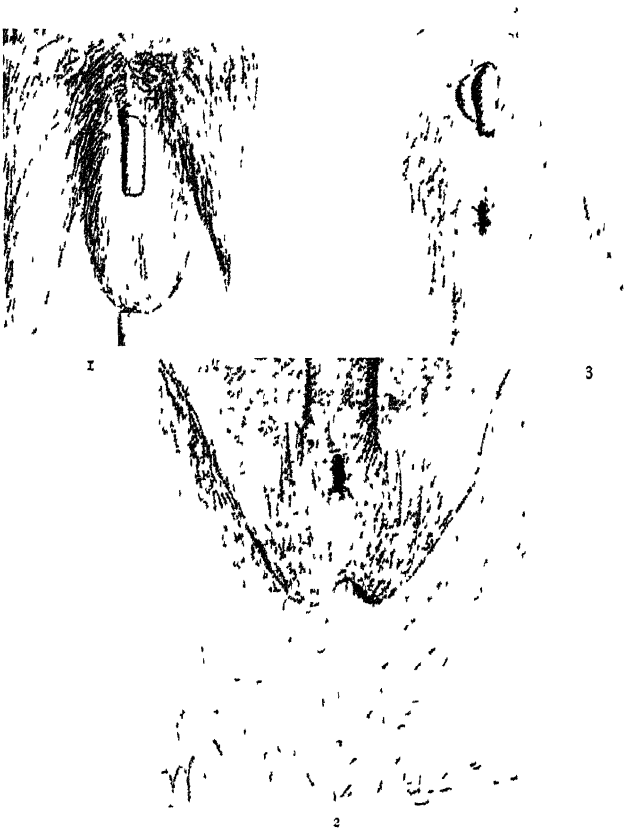


FIG 55 —To show the effect of transplanting the testes into a castrated female rat 1 Penis and scrotum of normal male 2 External genitals of normal female 3 External genitals of female with testes transplanted (Steinach)

developed and the normal sexual activity of the animal manifested itself

Pezard repeated Berthold's experiments on fowls and showed that a certain amount of testicular tissue is necessary to secure the development of the

sexual characters, but that anything more than this is superfluous The graft either produces a full effect or none, it is "all or nothing" in its action

Steinach not only grafted testes into castrated males but also into castrated female rats and guinea pigs, and showed that the secondary sexual characters are modified in the direction of maleness (Figs 54 and 55)

It has proved more difficult to get grafts of the testes to grow in castrated females than it is to get grafts of the ovary to grow in males

Pezard, Sand, and Caridroit[1] found that the effects of grafting testes in a fowl after partial oophorectomy was to produce a condition of redness and congestion of the comb resembling that of the cock, but no change in plumage Both ovaries and testes were active

Cases of successful transplantation of testes in man have been recorded, where the symptoms of castration have disappeared and sexual activity has reappeared In many of these cases the graft did not survive, and produced its effects only for a comparatively short time

These transplantation experiments, of course, at once dispose of the old idea that the gonads act reflexly through the nervous system They must act by passing something into the blood

5. Removal of Graft. The evidence afforded by castration and grafting is clinched by the crucial experi-

[1] *C R Soc Biol* 1924, 90, 1459

ment of removing the graft when the symptoms and signs of castration again manifest themselves

6. Extracts—Injection of. Injection of extracts of the testes were first shown by Nussbaum to be effective in causing the development of the clasping pad of the clasping reflex in castrated frogs His results have been confirmed by Steinach In castrated cockerels Pezzard records the development of the congested comb and wattles under subcutaneous administration of extracts of testes

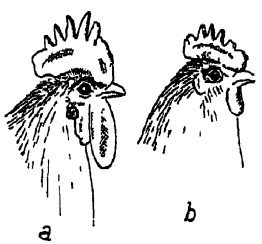


FIG 56.—Head of castrated cock after continued treatment with extracts of testes and after a cessation of this treatment (Pezard)

That the testes exercise an early influence upon the development of the secondary sexual characters even in intra-uterine life is indicated by the investigations of what is known as the "*free martin*" This condition is sometimes observed in the twinning of cattle, where one ovum develops into a male and the other into a female with secondary male characters Lillie has found in these cases that there is an anastomosis of the allantoic vessels due to a fusion of the chorionic vesicles Apparently the internal secretion from the testes of the male twin by passing in the blood stream to the female twin modifies the somal sexual characters (Figs 57 and 58).

The question must next be considered—Is the action of the testes on development due to the

whole organ, or to the tubular spermatogenic part, or to the interstitial cells? The evidence points conclusively to the interstitial cells This was

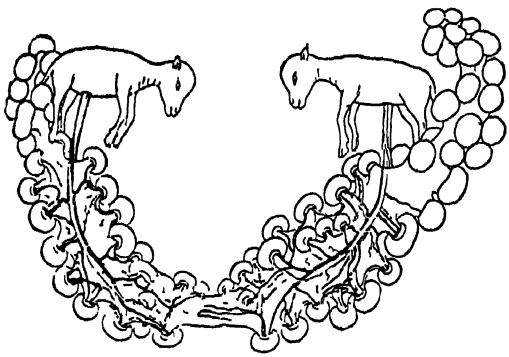


FIG 57.—Twin fœtal lambs, each with its separate circulation (Lillie)

first clearly proved by Shattock and Seligman by experiments on cockerels They found that, if the vasa deferentia be ligatured, spermatogenesis

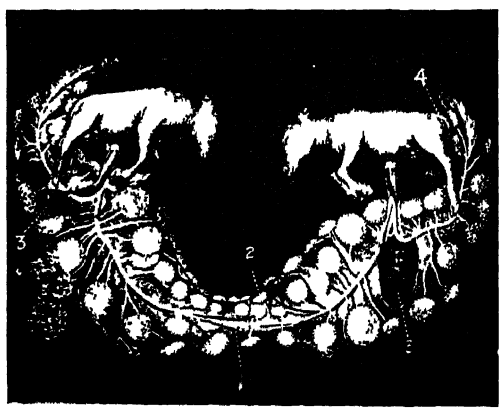


FIG 58.—Twin fœtal calves with anastomosis of the allantoic vessels (Lillie)

stops and the spermatogenic cells degenerate, but that the animal develops sexual characters The interstitial cells and the cells of Sertoli however persist

That the cells of Sertoli are not essential demonstrated by Bouin and Ancel in the They found that after ligature of the vas the cells also in time degenerate, leaving only the interstitial cells

The same evidence is afforded by the study of **Cryptorchidism**, where the testes remain unde-



Fig 59 —Cryptorchid testes of pig to show atrophy of tubules and increase of interstitial cells (Ancel)

scended into the scrotum The condition has been found in man, and it is fairly common in pigs The cryptorchid testes show no spermatogenesis but a great increase of the interstitial cells The animal is of course sterile, but it develops all the characters of a male (Fig 59)

In many mammals the testes descend from the abdominal cavity into a scrotum either during

each oestrus or once and for all before the onset of puberty This is probably correlated with their great increase in size Since the temperature in the scrotum is considerably lower than that of the abdominal cavity, since the undescended testis does not show spermatogenesis, and since some experimental work indicates that raising the temperature of the intra-scrotal testis to that of the abdominal cavity leads to a retrogression of the process of spermatogenesis, it has been argued that the testes pass into the scrotum because the lower temperature is more favourable to spermatogenesis But why should spermatogenesis go on actively in animals with intra-abdominal testes ? It seems more probable that, the testes having assumed the intra-scrotal position, spermatogenesis has become adapted to the temperature in that situation, so that it no longer proceeds normally at other temperatures

Lately Steinach, from experiments on rats and men, and others from similar experiments on the dog, have maintained that vasectomy is followed by the disappearance of the signs and symptoms of senescence and by a return of sexual competence If this be so, it is strong evidence in favour of the interstitial cells not only controlling development and growth, but of their exercising an important influence on the body and upon the sexual function throughout the whole of life (Figs 60 and 61)

Simpson and Marshall[1] found that after castration in the cat stimulation of the pelvic nerves



Fig 60.—Senile rat to left, same rat after vasectomy (Steinach)

(nervi erigentes) caused only a slight erection of the penis

The **action of X-rays** upon the testes gives further support to the conclusion The application of these rays leads to a degeneration of the cells of



Fig 61.—Testes of senile rat Testes of senile rat after vasectomy (Steinach)

the tubules and to an increase of the interstitial cells The subject becomes sterile, but retains sexual potency and all the secondary sexual characters which are lost upon castration

An extremely interesting phenomenon has been discovered in the case of the Sebright bantam cock

[1] *Q J Exp Phys* 1908, 1, 257

and in the Campine cock In these breeds the male is hen feathered, but upon castration the typical cock feathering of the tail and neck characteristic of other breeds appears

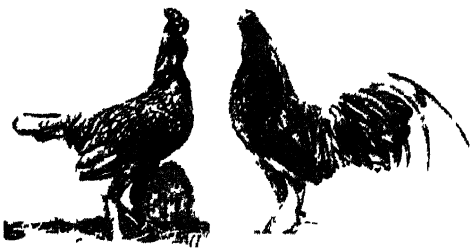


FIG 62 —Sebright bantam cock before and after castration (After Morgan)

There seems to be something in the testes which inhibits the development of these male characters Boring and Morgan have found that there are two types of interstitial cells—one small and one large, and resembling the luteal cells of the ovary This suggests, what has already been hinted at in considering determination of sex, that in every individual there may be two kinds of sex-determining cells, the one preponderating over the other In the Sebright and Campine cocks these female-producing cells appear to be sufficiently potent to check the characteristic development of feathers of the male In considering inter-sexual forms in

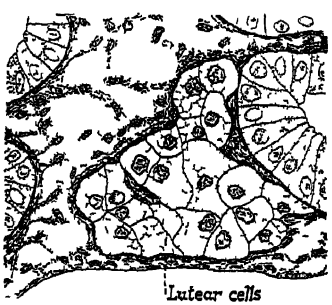


FIG 63 —Lutear cells in testes of Sebright bantam cock (Boring and Morgan)

insects it was shown that the structures latest developed were those which tended to show variation from the general sex pattern (p 104) The characteristic feathering of the cock is one of the latest developed of its characters

The existence of two kinds of interstitial cells in mammals is suggested by the observations of Wagner that in the testes of the mouse one set of cells takes up while the other does not take up "Pyrrholblau" administered during life

The mass of evidence pointing to the influence of the interstitial cells in controlling the growth and metabolism of the body raises the question of how it is possible to explain these cases of dissociation of gonadal and somal sex, *i e* cases with the body of a female and the gonads of a male, or of those with the body of a male and the gonads of the female (p 74)

First it should be recognised that these are exaggerated cases of what is of frequent occurrence, the manly woman and womanly man, extending even to their sexual proclivities May it be that they are to be explained in terms of the observations on the Sebright cock, and that in every animal there are the two types of sex-determining cells struggling for dominance?

INFLUENCE OF THE OVARIES UPON THE SOMA

In the human females at the time of birth the ovaries show huge numbers of small Graafian

follicles Waldeyer estimated that at birth the human ovary contained from 100,000 to 400,000 ova, while at puberty the number was reduced to 30,000 or 40,000

The question of whether oogenesis goes on after birth has recently been investigated by Papanicolaou[1] in guinea pigs, and he adduces evidence that fresh ova may originate till the end of sexual life

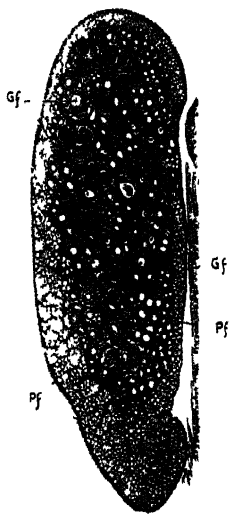


Fig 64 —Ovary of cat at time of birth (Bicdl)

In the human female sexual activity does not manifest itself till on an average about the fourteenth year of age In a certain number of apparently normal girls it appears earlier, in other cases somewhat later

During childhood growth is most active in the first year, and then decreases in rate as in boys, but a prepubertal increase occurs at an earlier age than in boys, from the eleventh to the twelfth year (Fig 47)

From about the ninth year the form of the body and the character of the child usually begin to show a difference from those of the male, but these differences become more and more distinct in the immediate prepubertal period

[1] *Proc Soc Exp Biol and Med* 1924, 21, 393

Examination of the ovaries throughout childhood shows no marked change till just before the onset of puberty, when the ripening of Graafian follicles begins

As puberty advances the somal characters of the mature female develop The breasts enlarge, the pelvis widens and flattens, pubic hair appears, and fat tends to accumulate, chiefly on the breasts and buttocks, and the uterus increases in size

1. Removal of Ovaries. That these changes are dependent on the development of the ovaries is shown by the effects of removal on account of disease in girls, and experimentally in lower animals The result is that the secondary sexual characters do not develop

But, while castration in boys leads to a persistence of the infantile type without an approach to the female, in woman and in some birds and mammals castration leads to the development of some of the male characteristics In birds, *e g* pheasants, fowls and ducks, the male plumage may be assumed (Fig 67) In hinds antlers may grow In women growth of hair on the face and the coarser skin and deeper voice of the male may develop

From such observations it is manifest that the ovaries determine the development of the secondary sexual characters of the females, just as the testes determine the appearance of the characters of the male But it must be remembered that similar changes have been found associated with hyper-

trophy or tumour growth of the inter-renal tissue in the cortex suprarenalis (p 156)

It has also been concluded from these results that the ovaries directly inhibit the development of male characters This conclusion seems less justifiable It may be that the ovary holds in check an influence of the inter-renal tissue to produce development of the male characters which is liberated when they are removed



FIG 65 —Castrated hen showing assumption of male plumage (Pezard)

2 The evidence of castration is perhaps supported by the occurrence of cases of **delayed sexual development** in which the ovaries have been found small and infantile in character But here a common factor, *e g* malnutrition, may influence body and ovaries together

3 **Pubertas Praecox.** On the other hand, certain cases of precocious sexual development in girls are apparently determined by premature growth of the ovaries, since some have been recorded where removal of a hypertrophic ovary has arrested the

development of such symptoms Verebely, quoted by Biedl, described the case of a girl who developed normally to her fifth year, when repeated vaginal haemorrhages began to occur The breasts enlarged and axillary and pubic hair grew A tumour was felt on the left side of the abdomen and on operation was found to be a sarcoma of the left ovary After its removal the signs of puberty gradually disappeared

4. **Transplantation of Ovaries** A successful graft of ovarian tissue is followed by the full development of



Fig 66 —To show the effect of transplanting the ovary into a castrated male guinea pig From left to right castrated male, normal female, feminised male and normal male (Steinach)

the secondary sexual characters and sexual activity This has been very clearly demonstrated in lower animals, *e g* in rabbits, and it has been found that removal of the graft leads to the usual changes which follow castration

Ovarian grafts have not only been made into the animal from which the ovaries had been removed and into others of the same sex, but in rats and guinea pigs they have also been made into castrated animals and even into uncastrated animals of the opposite sex (Fig 66).

Such grafts grow best when made from one of a litter into another member of the litter They are more generally successful than grafts of testes

The result of implantation into a castrated male rat is to feminise it The animal develops the more slender skeleton and the softer hair of the female The penis and prostate decrease in size Even in conduct it resembles the female in its behaviour towards males, apparently experiencing oestrus, and showing the characteristic mode of carrying the tail at that period and the characteristic kick of the hind leg on the approach of the male

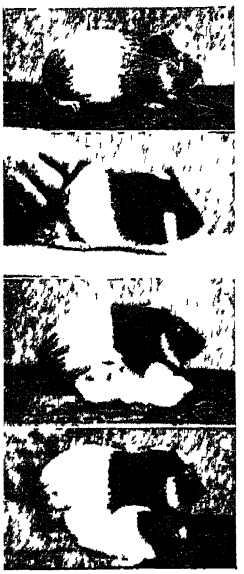


Fig 67 —From above, *a*, feminised male, *b*, showing penis of above, *c*, showing feminised male suckling one young, and, *d*, suckling two young (Steinach)

In the guinea pig the mammary glands show marked development and may secrete milk so that a young animal may be suckled (Fig 67)

When the ovary has been transplanted into an uncastrated male according to Sands' observations alternations of sex manifestations may occur (Fig 68)

There is a certain period of latency between the transplantation and the resulting action, and Lipschutz [1] finds that with ovarian grafts into the

[1] *C R Soc Biol* 1924, 90, 1410

kidney of partially castrated males the latency varies with the size of the graft and with the extent of the reduction of the testes There seems to be a struggle between the two internal secretions

In connection with ovarian transplantation the interesting question is raised, if the ovary or part of the ovary of one animal can be grafted upon another, can the graft functionate so as to produce

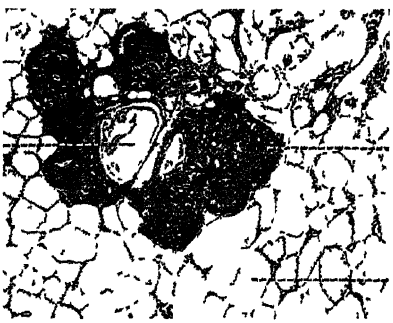


FIG 68 —Piece of ovary transplanted into testes (Sand)

ova which may be fertilized and may develop in the uterus of the host ? From the point of view of inheritance this problem is extraordinarily interesting, but it has not been fully investigated The results so far obtained rather favour the view that the ova produced in the transplanted ovary are uninfluenced by the foster mother Castle and Phillips transplanted the ovaries of a black guinea pig into a white animal This was impregnated by a white male In three pregnancies it threw black offspring (Fig 69)

Guthrie, who experimented on fowls, considers that the characters of the chicks showed an in-

fluence of the host, and he records a similar result in a guinea pig In the fowl the complete removal of the ovaries is difficult, and in guinea pigs, unless pure breeds are dealt with, the colour of the progeny is a precarious index of their origin

5 **Extracts of Different Parts of the Ovaries** Extracts have been used in gynaecological practice, but there is no definite evidence of their beneficial effect Experimentally it has been shown by Hermann that the ether extract of the corpus luteum when injected into young rabbits has a markedly stimulating effect upon the growth of ovaries, uterus, and mammary glands In castrated animals such injections prevent the atrophy of the uterus

The active substance has not been isolated, but Hermann found that it contained only C, H and O, and that it gave the reactions of cholesterol

Allen and Doisy[1] have recorded experiments showing that the liquor folliculi of the pig when injected into castrated female rats and mice induces oestrus This is considered more fully on p 178

In the male sexual desire and capacity for coition depends upon the interstitial cells, but in the female, as will be presently explained (p 178), another mechanism may play a part in determining the onset of oestrus

[1] *J Am Med Ass* 1923, 81, 819

The question of which part of the ovary—the ova, the cells of the granulosa or the interstitial tissue, plays the important part in determining the growth of the body and the condition of sexual activity is not so easily answered as in the case of the testis There, it will be remembered, all the

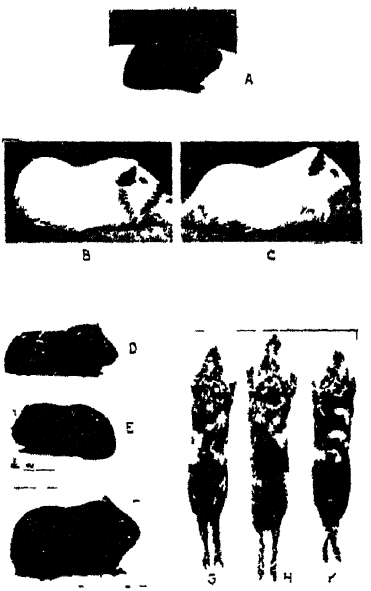


FIG 69.—Ovary of black guinea pig (A) transplanted into castrated white female (*B*) This when mated with a white male (*C*) produced black young—*D, E, F, G, H, K* (Castles)

evidence pointed to the interstitial cells as the active part

The existence of interstitial cells in the ovaries of many animals has been denied, and, while they seem to be enormously abundant in some animals, *e g* the rabbit, their origin has led to considerable dispute

Winiwarter and Louise MacIlroy maintain that they can be traced even in the human subject to the germinal epithelium which forms the Graafian follicles with their ova (Fig 41, p 117)

Others have adduced apparently satisfactory histological evidence that they are in part at least formed from some of the follicles It has been shown that by no means all of these follicles reach maturity, and that, even if they do so, they may not rupture to allow the escape of the ovum In these cases the ovum degenerates and the follicle collapses and atrophies, and cells either of the theca interna or of the granulosa thus come to lie apparently between the other follicles, so that they may be called the interstitial cells (Fig 44, p 119)

The two views of the origin of the interstitial cells are not mutually exclusive It may be that the greater number of the cells of the epithelial downgrowths first become follicle cells and later interstitial cells, while some may never get included in the follicle In either case their origin is the same, they are essentially of the same stock as the germ cells

While the **action of X-rays** on the testes, by destroying the intra-tubular cells and preserving the interstitial cells, demonstrated the importance of the latter, the influence of these rays on the ovaries seems to depend very much on the dose administered Small doses seem to increase the activity of the ovaries, larger doses lead to atrophy of the

follicles and of the interstitial cells and to the characteristic results of castration

The examination of grafts show that, for some time at least, oogenesis goes on, but after several months the growth of the follicles appears to be in abeyance and the interstitial cells alone survive Since in these cases the uterus shows no involution it has been argued that in the ovary as in the testes it is the interstitial cells which determine the characteristic growth

From the consideration of the action of the gonads upon growth and development, the conclusion thus seems unavoidable that, while the sex of the germ is determined by the metabolic activities of the parental gametes—whether the result of hereditary inertia or of the influence of factors external to the germ, the development of the secondary sex characters of the soma, anatomical and physiological, is dependent upon the germ cells or upon the ancillary cells which are related to them and which have probably the same origin

But this is not true in all animals Meissenheimer finds that castration of the caterpillar of moths and transplantation of the gonads of the opposite sex does not modify the development of the secondary sexual characters In these animals both gonadal and somal sex seem to be determined by the characters of the germ cells In them hereditary inertia is prepotent

The student should read

The Internal Secretion of the Sex Glands By Alexander Lipschutz. Hepper & Son, Ltd , Cambridge, and William and Wilkin Co , Baltimore 1924

CHAPTER VII.

INFLUENCE OF THE SOMA ON THE GONADS

It would be curious if the soma, thrown off as it is from the germ cells for their protection and nutrition, exercised no influence upon their parent cells which lie embedded in it

In the previous pages evidence has been adduced that the essential characters of the gonads may be modified by the condition of the soma Reference may be made to (1) The determination of sex in barnacles and also in bonellia (p 70) (2) The effect of feeding on the development or non-development of the ovary in the honey bee (3) The influence of temperature on the characters of the germ cells produced by *Talaeporia* (p 101) (4) The modification in the character of the eggs produced parthenogenetically by rotifiers by alteration in the feeding (p 80) (5) In vertebrates the observation by Champy of the atrophy of the testes of newts in starvation and the conversion of the gonad to an ovary on subsequent feeding and other evidence of sex reversal

In mammals the effect of alteration of the general nutrition is generally in the direction of

accelerating or retarding the growth and activity of the gonads This is more especially the case in the female There is evidence that when ewes are well nourished in autumn, when they are usually impregnated, twins are more generally produced than when their nutrition is defective During the Great War a decrease in ovulation and menstruation was correlated with the scarcity of food

But certain structures have a special action upon the gonads

Inter-renal Tissue—The Cortex Supra-renalis. As already indicated (p 116) there is evidence from the study of development that the cells of the inter-renal tissue have a similar origin to the germ cells, or at least to their ancillary cells, and hence, any influence which these structures may exercise upon the gonads should perhaps not be regarded as demonstrating an action of the true soma In fact Marine has proposed to call the inter-renal the para-sex tissue

Structurally the cells very closely resemble the interstitial cells of the gonads and especially of the testes Like them they are loaded with lipoids

This tissue is not confined to the supra-renal bodies, but is found scattered up and down the aorta, down the spermatic cord and into the broad ligaments of the ovaries In some animals these accessory masses are very abundant

The close relationship between the inter-renal tissue and the chromaffin tissue which constitutes

the central part of the supra-renals in mammals does not exist in all groups of vertebrates In birds the latter is not included in the former, and in fishes the two lie completely separate from one another

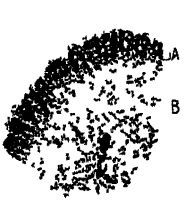


FIG 1



FIG 2

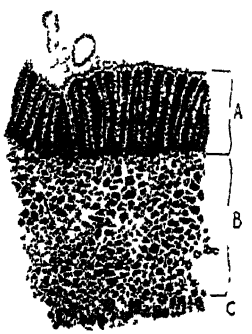


FIG 3

FIG 70.—To show changes of cortex supra renalis before and after birth 1 Foetus at 3rd month 2 Foetus at 7th month 3 Child 12 days old (Armour and Elliot)

Before birth inter-renal tissue in the cortex supra-renalis is very abundant, but after birth it decreases in amount till adult life is reached During the second week of life the two deepest layers undergo a curious process of involution, which coincides with an increase in the basal metabolism of the infant This is of interest, since it will be afterwards shown the removal of the cortical tissue is followed by increased heat pro-

duction if the thyreoid is intact Regeneration occurs later from the external layer of the zona granulosa It is interesting to correlate these changes, described by Armour and Elliot,[1] with the changes in the interstitial cells of the testes of the horse after birth (p 123)

Physiology. In mammals removal of the inter-renal tissue without injury to the chromaffin tissue in the supra-renals has proved very difficult to accomplish, and the existence of accessory masses may compensate for the tissue which has been removed

In fishes Biedl has taken advantage of the two structures lying independently to remove the mass of inter-renal tissue He states that the fish becomes weaker and finally dies

In mammals complete removal of the supra-renals generally leads to emaciation and death That this result is not due to the removal of the chromaffin tissue of the medulla is indicated by the fact that destruction of the central part of the glands by thermocautery is followed by no untoward result (Vincent)

Considerable destruction of the inter-renal tissue of the cortex is followed by an increased heat production provided the thyreoid gland is intact

Jaffe and Marine [2] record a series of experiments on the effects of removal and extensive injury of the supra-renals on the ovaries and testes of

[1] *J Path and Bact* 1911, 15, 481
[2] *J of Exp Med* 1923, 38, 93 and 107

rabbits While these removals were followed by hypertrophy of the interstitial cells of the ovaries, which became more marked the longer the animal survived, they were not associated with definite changes in the testes It is difficult to explain why removal of a tissue which, as will be presently seen, seems to form a product which influences growth towards masculinity should be followed by an hypertrophy of the interstitial cells of the female and not of the male It may be that the inter-renals exert an inhibitory influence on those interstitial cells which determine the development of female characters (p 138)

From his own experiments, and from the examination of the work of others, G N Stewart [1] concludes that, while the chromaffin tissue is quite unessential for the continuance of normal life, the inter-renal tissue is essential Removal in mammals generally leads to no manifest symptoms for some time , then the animal refuses food, becomes weaker and dies How the inter-renal tissue acts is, according to him, unknown

The effect of feeding inter-renal tissue upon the gonads has been studied by R G and A D Hoskins They found that the testes showed increased growth, and that in a few cases the ovaries were larger than in the control animals

That there is a reciprocal action between the inter-renals and the gonads is indicated by the fact

[1] *Physiological Reviews*, 1924, 4, 163

that removal of the ovaries is followed by hypertrophy of the supra-renal cortex in rabbits, guinea-pigs and dogs, and that in pregnancy in rabbits an enlargement of the cortex takes place along with an enlargement of the interstitial cells of the ovaries (Lane Claypon) A similar increase in the cortical tissue has been described after castration in the male in the same animals

Clinical observations point to some relationship between this tissue and development and growth. Glynn concludes that hypertrophy is associated with premature sexual development in the male, and with the assumption in the female of male characters, such as the characteristic growth of the hair and more marked muscular development

Marine, Manley and Baumann[1] find that in rabbits removal of the gonads leads to a persistence of the thymus gland—a fact already established by Henderson[2] and by Goodall[3] and others Marine and his co-workers further find that removal of the supra-renals not only retards involution of the thymus but actually causes regeneration A combination of suprarenalectomy and gonadectomy has a still more potent influence Curiously enough, while removal of the thyreoid accelerates involution of the thymus, the effects of gonadectomy and of suprarenalectomy does not occur after the thyreoid is removed

[1] *J of Exp Med* 1924, 40, 424 [2] *J of Phys* 1904, 31, 221.
[3] *J of Phys* 1905, 32, 191.

They thus establish an interesting relationship between the thymus and the gonads, a relationship which was suggested by my observation of the effects of simultaneous removal of the thymus and testes, which I found leads to a retardation in the growth of young guinea pigs, so that they require a prolonged period to reach the weight at which sexual maturity should occur (p 125) These results seem to indicate that both thymus and gonads play a part in determining growth, and that when one is removed its removal is compensated for by the increased action of the other

The Thyreoid[1] The thyreoid gland in all vertebrates takes origin as a hollow outgrowth from the ventral wall of the anterior part of the pharynx In the human subject in the embryo of 5 cm in length the pouch has begun to expand laterally Later it consists of two hollow vesicles still connected with the buccal cavity by a duct After the fifth week the duct becomes obliterated and the vesicular part rapidly increases

The association of the thyreoid with the gonads is indicated by the enlargement which occurs in women at the menstrual period and in pregnancy

That the thyreoid has an influence on the development of the gonads is also shown by the effects of removing it in very young animals, and

[1] I deliberately adhere to the Galenic spelling The cartilage of the larynx was called *θυρεο ειδής* from its resemblance to a shield, and the gland should be the thyreoid, not thyroid *Θυρα* is an opening, hence the pelvic foramen was called *θυρο ειδής*

still more by the condition of children in which it has failed to develop—*cretinism* The result is a non-development of the gonads and a persistence of the infantile type of body and features The rate of metabolism is lowered often as much as 40 per cent , the temperature tends to be low , the

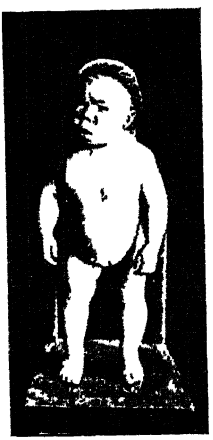


FIG 71A —A female cretin of 15½ years of age

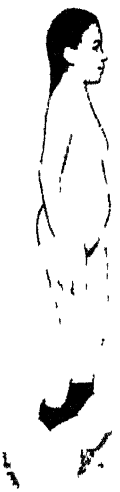


FIG 71B —Same case at 21½ years after treatment with thyroid extract (Weygandt)

intelligence remains undeveloped, and the bones formed in cartilage develop so slowly that the length of the limbs is markedly decreased and the stature is stunted The intra-membranous bones do not participate in this delay, and hence the bones of the cranial vault tend to arch forward and to give a peculiar appearance to the physiognomy (Fig 71A)

Balzac in his *Le Medecin de Campagne* has given the most vivid description of an aged cretin

" Le crétin était la seule variété de l'espèce

humaine que le chef d'escadron n'eut pas encore vue A l'aspect d'un front dont le peau formait un gros pli rond, de deux yeux semblable à ceux d'un poisson cuit, d'une tête couverte de petits cheveaux rabougris auxquels la nourriture manquait, tête toute déprimée et denuée d'organes sensitifs, qui n'eut pas éprouvé, comme Genestas, une sentiment de dégoût involuntaire pour une créature qui n'avait ni les grâces de l'animal ni les privilèges de l'homme, qui n'avait jamais eu ni raison ni instinct, et n'avait jamais entendu ni aucune espèce de langage "

The influence of the thyreoid upon the gonads appears to be more direct in the female than in the male Hammett [1] finds that in young albino rats removal of the thyreoid reduces the growth of the testes to only 51 per cent of the normal, but brings about retrogressive changes in the ovaries, so that weight is actually lost It is interesting to note that he finds that the decrease in growth of the brain of the female is much greater than that of the male

On the other hand, Allen [2] finds that removal of the thyreoid in tadpoles delays the metamorphosis of the body, but does not delay the development of the germ cells in the gonads Further, thyreoid feeding, while greatly accelerating metamorphosis, has no influence on the sex glands [3] (Swingle)

[1] *J of Heredity*, 1923, 14, 291 [2] *J of Exp Zool* 1917-18, 24, 499
[3] *J of Exp Zool* 1917-18, 24, 521

A possible relationship of the thyreoid with sex determination is suggested by some observations of Parhon and Marza[1] In female rabbits deprived of the thyreoid he found a higher proportion of males —fifteen males and five females against six males and eight females in normal rabbits In young guinea pigs from both parents thyreoidectomised the proportion was six to six

They recall the observation of Witschli and of Adler The former found in the frogs of the Ursprungtal thyreoids resembling those of Basedow's disease and a great preponderance of males The latter found that frogs from eggs fertilized in a condition of super-maturation were nearly all male and showed similar changes in the thyreoid

The changes in the body produced by non-development or removal of the thyreoid in the young are not similar to those produced by castration (p 126), and hence the condition of the gonads are not correlated to the condition of the body through their relationship to the thyreoid

Thyreoidectomy is followed by hypertrophy of the true pituitary body This is of special interest because of the close relationship of this structure with the gonads

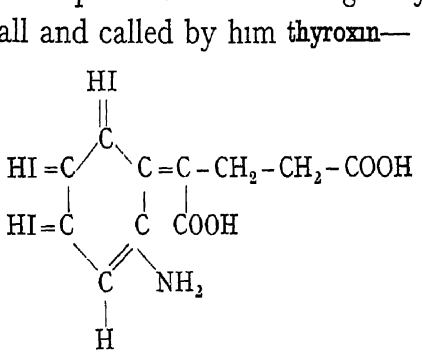
The evidence that the thyreoid is a structure essential for proper growth and development of gonads of the body is substantiated by the fact first demonstrated by Schiff (1884) that a suc-

[1] *C R Soc biol* 1924, 90, 323

cessful graft of its tissue will prevent the onset of the symptoms caused by removal, or, if they have supervened, will lead to their disappearance Removal of the graft leads to recurrence of the symptoms

Not only do grafts act in this way, but, as Vessale and Gley showed, the subcutaneous administration of extracts of the gland, and, as Murray demonstrated, the administration of the gland or its extracts by the mouth have a similar action

The product of the thyreoid which manifests this action is a complex iodine-containing body isolated by Kendall and called by him **thyroxin**—



It is apparently an iodised derivative of tryptophane, and it may exist in four different conditions

The thyreoid contains a higher proportion of iodine than any other tissue of the body, and it has an enormous power of accumulating iodine, which it gradually elaborates into the active thyroxin Normally it contains about 1 mg per gram of fresh substance

The amount of iodine in the gland is correlated

with its structural appearance When it falls below 0 1 per cent of the dry weight hypertrophic changes manifest themselves

Administration of salts of iodine do not act in the same way as do extracts of thyreoid, so it must be concluded that in the gland the iodine is synthesised into an active compound

It is true that some of the actions of the thyreoid may be performed by salts of iodine Stuber and his co-workers [1] showed that the process of methylation of guanidin-acetic acid to creatin does not occur after the removal of the thyreoid, but that the power may be restored by administration of iodine

Swingle [2] finds that there is evidence that the action of thyroxin upon development of tadpoles is dependent upon a different part of the molecule to that which accelerates metabolism By replacing an H in the imino group with acetyl the influence on mammalian metabolism is abolished, but the effect on growth remains, while the effect on growth is produced as well by di-iodotyrosin, which has not the CONH molecule as by thyroxin. This effect is due to the iodine linkage

The main action of the thyreoid on the gonads and body, however, depends upon the formation of a specific product, and the administration of thyroxin produces all the effects characteristic of thyreoid extracts

[1] *Bioch Ztsch* 1923, 143, 221

[2] *Endocrinology*, 1924, 8, 832

How far it acts directly upon the tissues or influences them through the nervous system cannot be considered as settled Thyroxin, as well as impure compounds containing it, *e g* iodothyreoglobulin, activate the endings of the true and false sympathetic nerves, and thus increase the stimulating action of adrenalin on the vagus or of the sympathetic (Ostwald)

The functional activity of the thyreoid must be independent of the nervous system, since it is adequately carried out by grafts But the discharge of thyroxin seems to be in part controlled by nerves, since stimulation of these leads to a decrease of the iodine content of the gland

A question of great interest is at what period of foetal life does the thyreoid become active and produce its characteristic product Fenger[1] found iodine in the thyreoid of ruminant embryos at the sixth week with a marked increase at the fourth month Hogben and Crew,[2] using the development test, found that it was active in sheep at the third month and in oxen at the fourth month Apparently the structure begins to function at a date later than the development of the gonads

The Pituitary. The pituitary of the anatomists consist of a downgrowth of modified nervous tissues from the floor of the third ventricle, the posterior lobe, and of the hollow upgrowth from the roof

[1] *J Biol Chem* 1912, 11, 489, and 12, 55
[2] *Brit J of Exp Biol* 1923, 1 1

of the mouth which forms the anterior lobe or true pituitary and embraces the former. It becomes separated from the buccal cavity, and consists of a pars intermedia closely applied to the posterior lobe, a cleft which is the remains of the lumen of the hollow upgrowth and a more massive pars anterior (Fig 72)

The true pituitary is enormously vascular It consists of two types of cells (1) The chief cells



Fig 72.—Pituitary of the cat The dark part is the *true* pituitary (Herring)

which are large and do not stain readily, (2) the chromophil cells which contain granules which stain deeply, some with acid, some with basic stains

This structure, lying as it does in the sella turcica of the basi-sphenoid, is difficult to remove

Two modes of approach have been used, one through the roof of the mouth, which renders asepsis impossible, and the lateral method by an extensive dissection down to the basi-sphenoid and then trephining the side wall of the sella. This has

proved the more satisfactory procedure Naturally the mortality for either of these operations is high

Successful removal of the posterior lobe produces no manifest results Removal of the anterior lobe in young dogs produces a marked slowing of the rate of metabolism, a tendency to lay in fat and arrested development of the gonads But the impaired growth of the long bones so characteristic of removal of the thyreoid is not present



Fig 73 —Case of dystrophia adiposogenitalis (Cushing)

A syndrome of symptoms first described by Dercum have been related to the non-development of the pituitary The condition is sometimes known as *dystrophia adiposogenitalis* It is characterised by a persistence of the infantile type, with general adiposity and a non-development of the gonads and secondary sexual characters (Fig 73)

Just as a eunuch is not always fat, so children with undeveloped pituitaries do not always develop adiposity Some cases occur (Lorrain's syndrome) in which fatness is absent, but in which the genital hypoplasia is present

Another pathological condition—*acromegaly*—is associated with changes in the pituitary

This condition is characterised by a slowly progressing overgrowth of the fibrous tissues and

bones The supraciliary ridges, the nasal bones and the lower jaw becomes much enlarged, while the subcutaneous tissues are thickened The very characteristic facies is developed The bones of



Fig 74 —To show the development of acromegaly (Cushing)

the hands and feet enlarged, and the hands are large and spade like (Fig 71)

Harvey Cushing has divided the progress of the disease into two stages, the first associated with



Fig 75 —Changes in testes in different stages of acromegaly (Cushing)

irritation and stimulation of the pituitary generally by tumour growth, the second associated with destruction In the first stage premature development of the testes has been recorded, in the later stages the gonads show atrophic changes (Fig 75)

The close interrelationship of the gonads, thyreoid and pituitary, is indicated by the facts (1) that castration of male and female animals is followed by hypertrophy of the pituitary, chiefly of the eosinophil cells, (2) that pregnancy is accompanied by enlargement of the chief cells, (3) that thyreoidectomy is accompanied by retrogressive changes in the ovaries and by hypertrophy of the pituitary, and (4) that decreased functional activity of the pituitary is accompanied by decreased growth of the gonads

A compensatory hypertrophy of the thyreoid after removal of the pituitary has been described, but this does not apparently prevent the development of symptoms Attempts to prevent the results of removal by grafts have so far not been successful, nor has the administration of extracts been of any benefit

Some experimenters, *e g* Bailey,[1] have questioned whether the symptoms are due to removal of the pituitary, and have maintained that they occur when the subthalamic part of the brain is injured, a region in which central synapses for important general somal reflexes occur The more recent work of Dott, however, seems to show that when the operation is performed so as to leave the subthalamic region uninjured, the characteristic symptoms are produced, and thus to relate them specifically with the pituitary

[1] *Ergebn d Phys* 1922, 20

There is no evidence as to when the true pituitary begins to function in foetal life, although some evidence is forthcoming that the internal secretion which passes through the posterior lobe may be demonstrated at about the third month in sheep and oxen

Uterus. The uterus is a secondary sexual organ of purely somal development There is some evidence that it exercises an influence on the gonads

Leo Loeb[1] found that removal of the uterus led to a persistence of the corpus luteum in guinea pigs for from sixty to eighty days On the other hand ovulation in young animals was not interfered with, and the corpora lutea were formed and persisted During the persistence of these, ovulation did not occur and the mammary gland developed

The Thymus. The thymus develops on each side as an epithelial outgrowth from the branchial clefts Each outgrowth branches freely, and finally becomes broken up into a network with islands of cells here and there, the so-called Hassal's corpuscles In the network lymphocyte-like cells make their appearance, which according to the observation of Hammar are true lymphocytes which invade the network from without, but which Stork has maintained are budded from the epithelial cells of the meshwork They seem

[1] *Proc Soc Exp. Biol and Med* 1923, 20, 443

to vary in abundance with the state of nutrition to such an extent that the size of the whole gland varies and may almost be taken as a measure of the general nutrition in childhood

The thymus is mainly a foetal organ, and it reaches its greatest size in relation to the size of the body at or soon after birth But it goes on growing till puberty is reached After this it begins to atrophy and is invaded by fibrous tissue and fat Thymus tissue may, however, be detected to the end of life (Fig 48 p 124)

Its probable reciprocal relation with the testes in determining growth in young and immature animals and its persistence after castration have been dealt with on p 125 (Fig 49), while its relationship to the cortex supra renalis—the para-sex gland of Marine has been considered on p 156

Marmorston, Gottisman and Jaffe[1] found that in rats before puberty removal of one lobe led to hypertrophy of the other

It is manifestly a prepubertal organ which co-operates with the testes and inter-renal tissues in determining somal growth

The Pineal Gland The epiphyses, or pineal body, is developed as a hollow outgrowth from the upper aspect of the third ventricle, and it lies in front of the superior corpora quadrigemina It is a small reddish body, and it is composed of

[1] *J Exp Med* 1925, 42, 413

spherical and tubular follicles filled with epithelial cells, sometimes containing calcareous matter

In some lower vertebrates, lampreys, some lizards, etc , it forms a third eye, and this probably explains its connections with the thalami

The evidence as regards its functions is mostly negative Exner and Boses,[1] using rabbits, found nothing abnormal after complete removal of the structure Foa [2] and others attributed to it an inhibitory influence on the growth of the primary and secondary sexual organs, basing their conclusions on the effects of removal in fowls Kolmer and Lowy,[3] using rats, found that removal produces no changes in the sexual organs, in growth, or in the development of fat, and these findings have been recently confirmed by E Hofmann [4] The evidence so far adduced gives no support to the theory that it exerts any influence on the sexual organs

Aschner [5] maintained that castration in various species and pregnancy in the human subject are accompanied by atrophy of the pineal But others have failed to confirm this, and Pellegrini states that there is rather an hypertrophy than an atrophy of the structure [6]

[1] *Disch Zeitsch f Chir* 1910, 107
[2] *Arch Ital d Biol* 1912, 57, 233
[3] *Pflug Arch* 1922, 196, 1
[4] *Pflug Arch* 1925, 209, 685
[5] *Zbt f Gyn u. Geburt* 1913, 1, 774
[6] *Arch p la Sc Med* 1914, 385, 121

The theory of Marburg[1] that the pineal has to do with temperature regulation is not supported by the experiments of Hofmann (*loc cit*), who found that in rats exposed to changes of temperature the adjustment was as good after as before removal of the pineal Hofmann concludes that there is no evidence that the pineal has any influence on the gain in weight or length, or in the development of fat or in the condition of the sexual organs The only suggestion of such an action which he found was an increase in the size of the seminal vesicles—a finding which he considers should be re-investigated

The interstitial cells of the gonads with the inter-renal tissue, the thymus, thyreoid and pituitary all seem to exercise an influence on the germ cells as well as on the somal cells to bring about a harmonious and co-ordinated development A disturbance in any one may be compensated for by increased action of others, as is seen in the increased size of the thymus in gonadectomy or reduction in the amount of the inter-renal tissue The co-operative action of the inter-renal and thyreoid is shown by the work of Marine, Jaffe and their associates, while the inter-relationship of thyreoid and pituitary has for long been known There can be little doubt that the adaptation of correlation between these structures is very per-

[1] *Ergebn d inn Med u Kinderheilk* 1913, 19, 146

fect, and that only when this is upset are the effects of disturbances of any one set of endocrinetes manifested

How these structures co-operate to bring about this regulation of development is still unknown, but the work of Lipschutz on the antagonism of the internal secretions of the ovaries and testes seems to indicate that there is a balanced interaction between their activity Whether this is through the nervous system or direct can only be conjectured

Further, we still require more information as to the extent to which the nervous system is involved in the actions of these secretions on the various parts of the body

In a previous publication (*Regulators of Metabolism,* Macmillan & Co , 1913) I ventured to represent these inter-relationships in a series of diagrams which, although very crude, possibly served to indicate some of the inter-relationships

CHAPTER VIII

SEXUAL LIFE

As already indicated, somal cells are thrown off from the germ cells in each generation for their nourishment and protection, and in all the higher animals the germ cells themselves lie dormant as regards their sexual activity during the growth and development of the body, but the gonads through their interstitial cells exercise a directive influence upon the lines of development (p 121) In many of the lower forms reproductive activity may be manifest even from a very early period of growth Generally it is in males that this early development occurs, *e g* the salmon par develops mature testes and may fertilize eggs In animals with alternating sex, *e g* the spider crab (*Inachus*), the male condition may precede the female (p 69)

In higher animals, even when growth is completed, the reproductive function is not always in evidence Periods of rest occur during which the nutrition of the soma and of the gonads is dominant In some animals the alternation between periods of sexual rest and sexual activity are sharply defined

During the former the animal behaves like a eunuch, during the latter its character completely changes, in many cases feeding ceases altogether, and the whole life is devoted to the exercise of the reproductive function

Male. In man from puberty to old age potential sexual activity exists This potential activity increases to reach a maximum in early manhood, after this it wanes, but, as Mott has shown, spermatogenesis goes on even in old age

In some animals the somal metabolism undergoes marked changes before the breeding season, leading to the development of antlers in stags or of breeding plumage in many birds, and to a complete change in the disposition of the animal

Since these changes do not occur after castration they must be due to the influence of the testes, which towards the breeding season may increase enormously Thus in the greenfinch they increase seven or eight-fold in diameter (Watson),[1] and in the mole two-fold in length and breadth (Tandler and Gross)[2] The tubules enlarge and spermatogenesis becomes active, and, as a result of this enormous increase in the tubules, the interstitial cells become less prominent But since sexual desire and sexual activity are manifested in animals after the tubules have been destroyed by X-rays and in cryptorchids, it must be concluded that

[1] *J of Phys*, 1919, 53, 86

[2] *Arch of Entwickl d Organ*, 1911-12, 33, 297 and 132

these are controlled by the interstitial cells The condition of these cells throughout the oestrous cycle has been studied by Tandler and Gross in the mole and by Watson in the greenfinch, and it has been shown that they reach their maximum prominence before ripening of the sperms begins

Female. The age of the onset of sexual life may be influenced by external temperature, as was demonstrated by Steinach and Kammerer in rats In the human subject the onset of menstruation varies with the latitude In Christiania it occurs on the average at seventeen years, in Algiers and Egypt at twelve-and-a-half years, but in this difference of race as well as of climate probably play a part The average age is about fourteen.

The onset of sexual life is characterised in most animals by recurring periods of oestrus or heat, during which the sexes are mutually attracted and coitus occurs In the human female sexual life is marked by the onset of menstruation, the discharge of a blood-stained fluid from the vagina This recurs at intervals which are usually at first irregular, but later become regular every twenty-eight days in the majority of women

The menstrual cycles in women and the oestrous cycles in lower animals continue for a varying time, which depends upon the duration of life of the animal In the human female the former continues till about the age of forty-five, when it tends to become irregular and finally ceases

THE OESTROUS CYCLE

While lower animals manifest sexual desire only during oestrus, the human female may experience it at any part of the cycle

The human menstrual cycle can be understood only in the light of our knowledge of the oestrous cycle in lower animals The duration and character of this varies enormously In some animals, *e g* birds, it recurs definitely at long intervals, and there is a long anoestrus during which the animal is practically sexless, and a short oestrus during which it is sexually alive

In others, *e g* the sheep, oestrus may be interrupted by short anoestrous periods, for which the name of dioestrus or metoestrus has been suggested

These two types may be represented as follows

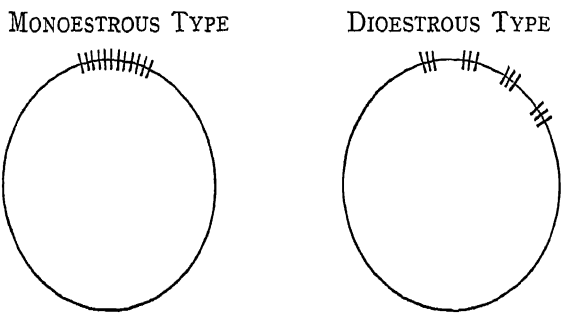


FIG 76 —To show different forms of oestrous cycle

Between them there appears to be no essential difference In the domestic pig oestrus occurs every three weeks all through the year, and the intervals may be called either dioestrus or anaestrus In rats and mice it occurs every four to six days

The oestrous periods are preceded by changes in the ovaries, in the uterus and in other organs, and they are correlated with the growth of the Graafian follicles One or more of these rapidly enlarge, and there is a great proliferation of the cells of the granulosa and of the theca interna, the latter changing from spindle-shaped cells to large epithelioid cells The cells of the discus proligerus become looser and liquor folliculi is formed in varying amounts (Fig 42, p 117)

The evidence that the condition of the follicles determines the onset of oestrus is fairly conclusive Marshall finds that in the dog, if the developing follicles be punctured, oestrus does not occur Allen and Doisy[1] state the injection of the liquor folliculi of pigs and cattle into castrated female mice and rats produces full oestrus in from forty to forty-eight hours, and that the mammary glands enlarge They also find that the administration of the fluid hastens the onset of puberty The investigation of Courrier[2] on the Bat, *Vesperugo pipistrillus*, confirm the observation recorded by Duval[3] that these animals, or at least the mature females, copulate in autumn, but do not ovulate till spring—after nearly seven months At the time of copulation the follicles of the ovary are not distended with fluid All through the winter the mucous membrane of the Fallopian tubes and

[1] *Endocrinology*, 1923, 7, 725 [2] *C R Soc Biol.* 1922, 87, 1365
[3] *J du l'Anat et de la Physiol* 1895, p 93

uterus are in a condition resembling that of oestrus and yield a secretion, possibly for the nourishment of the masses of spermatozoa which lie in the uterus The vagina shows an epithelial proliferation followed by keratinisation which blocks the passage Courrier argues that the ripe follicle is not the cause of oestrus, but it seems possible that in these animals the secretion of the follicle instead of accumulating may be rapidly absorbed to produce its action

Stockard has shown that not only is there an increased vascularity of the mucosa of the Fallopian tubes and uterus, but that there is a proliferation of the epithelial cells of the vagina, so that the onset of oestrus in guinea pigs, rats and mice may be determined from the examination of vaginal smears

The Graafian follicle expands on to the surface of the ovary and finally ruptures, discharging the ovum with some of its surrounding cells of the granulosa into the peritoneal cavity In some animals—rabbit, cat and ferret—rupture of the follicle does not take place unless coitus occurs The trumpet-like end of the Fallopian tube is closely applied to the surface of the ovary, and the escaped ovum is caught in it and transmitted to the uterus (p 196) Chemiotaxis seems to play a part in this passage of the ovum into the tube, and when one tube has been removed in ruminants there is evidence that the ovum may occasionally cross the peritoneal cavity and enter the opposite tube

In the tube the ovum may be met by spermatozoa and there fertilized If it is not, it begins to degenerate as it passes on down the tube In most animals the passage of the ovum to the uterus takes about four days, in some animals it may take longer From observations on the guinea pig and rabbit it appears that the ovum remains unattached in the uterus for about another six days

After the rupture of the follicle there may be a haemorrhage into the empty space, but in some animals, *e g* the mouse, this does not occur The most important change is an enlargement of the cells of the granulosa which thus fill the empty follicle, and at the same time a regression in the cells of the theca interna Their fate has not been clearly determined

A corpus luteum is thus formed, which at first shows a red patch at its point of rupture due to vascular engorgement Gradually it enlarges and becomes firmer and the cells become loaded with yellow coloured lipoids

Its future history depends upon whether the ovum has or has not been fertilized In the latter case it begins to degenerate in about fifteen days in the pig, rabbit, and guinea pig, or after thirty days in the dog, and at the next menstruation in the human subject In all animals it continues to grow for a period sufficient to allow time for the ovum or ova to reach the uterus

If the ovum be fertilized the corpus luteum

continues to grow, attaining its maximum in about three months in the human subject, and it persists till the end of pregnancy, when it degenerates

Correlated with these changes in the Graafian follicle, marked alterations in the mucous membrane of the uterus occur These have been most fully investigated in the pig, which manifests oestrus at intervals of twenty-one days

With the pre-oestral growth of the follicles active mitosis occurs in the cells of the endometrium, and when the corpus luteum is formed and the ova have passed down the tubes into the uterus, the epithelial lining cells assume a columnar arrangement and then show cytoplasmic processes on their surface This continues till, if the ova are fertilized, their chorionic processes become attached This occurs in about thirteen days The ovum reaches the uterus in the four to six blastomere state in about four days, and the chorionic villi are formed when it is in the shield stage Changes similar to those which occur in pregnancy take place, *even if the ova have not been fertilized*, but in this case the corpora lutea retrogress about the fifteenth day and the uterine mucosa returns to the pre-oestrus condition

The very superficial character of the changes in the uterus of the pig is probably to be explained by the very loose and superficial connection which the embryo forms with the maternal mucosa

Hill and Donoghue described similar changes in

the uterus of the marsupial *Dasyurus Viverrinus*, which has one oestrus in the year followed by ovulation, the early changes occurring whether impregnation takes place or not It was they who first described these changes in the absence of impregnation as a " pseudo-pregnancy "

In the rabbit, in which ovulation only occurs with coitus, Ancel and Bouin found that, if coitus with a buck sterilized by vasectomy was allowed, corpora lutea were formed, and that although the ova were not fertilized, all the changes in the uterus characteristic of early pregnancy occurred

The close correlation between the changes in the follicles and the uterine mucosa is thus established

Is there a causal relationship between these changes in the corpora lutea on the one hand and the changes in the uterus on the other? L Loeb found that in guinea pigs irritation of the uterine mucosa by the insertion of a foreign body, or even by scratching it on the seventh day after a coitus without fertilization, when implantation of fertilized ova ought to occur, leads to a growth of the endometrial tissue such as occurs in pregnancy This could be induced only at this period after ovulation, and it could not be produced if the ovaries had been removed or the young corpora lutea cauterised These observations have been confirmed by others

It is thus evident that the changes in the uterus are secondary to changes in the follicles and are

dependent upon the formation of the corpora lutea They are manifestly changes preparatory to the attachment of the ovum to the maternal mucosa That the corpora lutea play an important part in securing this implantation was demonstrated as far back as 1903 by Fraenkel By experiments upon rabbits he showed that if the ovaries are removed or the corpora lutea destroyed within six days after ovulation, implantation of the ova does not occur

During the persistence of the corpus luteum in most animals further ovulation does not occur Haberlandt[1] states that injection of extracts of the ovaries, including corpora lutea, and of the placenta of pregnant animals, inhibits ovulation in rabbits, and he correlates this with Fraenkels' old observation that the persistence of a corpus luteum in the cow may prevent the development of oestrus The products of non-pregnant ovaries have not this action

Leo Loeb[2] clearly differentiates between the influence of the developing follicle and of the corpus luteum The former, by an internal secretion, calls forth proliferation of the uterine wall, vagina and mammary gland, and apparently induces oestrus With the onset of oestrus changes in the vagina stop, but they continue in the mammary gland

[1] See *Berichte u d ges Phys* 1924, 24, 491

[2] *Proc Soc Exp Biol Med* 1923, 20, 443

Between this influence of the follicle and that of the corpus luteum there is an intermediate stage during which degenerative changes may occur

As the corpus luteum develops it sensitizes the lining membrane of the uterus for the fixation of the ovum, it prevents ovulation and the onset of oestrus, and it stimulates the growth of the mammary gland

He classifies the stages of the oestrus cycle as follows

I Follicular Phase
  (*a*) Pro-oestrus
  (*b*) Oestrus
  (*c*) Metoestrus (in some cases)
II Intermediate Phase
III Lutein Phase (Corpus luteum)
  (*a*) Period of Sensitization of Uterus
  (*b*) Period of return to resting state
  (*c*) Period of resting state

THE MENSTRUAL CYCLE

The difficulties of explaining the phenomena of the sexual cycle in woman in terms of these observations on lower animals are considerable Only in man and in the higher apes is there the marked regular menstrual bleeding

In the first place there is no true oestrus A mass of statistics collected in Germany during the war tend to show that fertile coitus may take place at any period of the menstrual cycle except

possibly for a week preceding the menstrual flow. This may be explained by the arrival of the ovum in the uterus after menstruation has commenced

While it is comparatively easy to examine the ovaries, uterus, and other sexual organs in lower animals at all periods of their oestrus cycle, this, of course, is impossible in the case of the human subject Hence, opportunity has had to be taken of the chances afforded by cases of abdominal operations at known dates between the menstrual periods

It is indeed surprising that, since the first series of such observations were made by Leopold in 1883, such a mass of material has been collected and investigated Leopold's naked eye examination of the ovaries led him to believe that ovulation might occur at any time in the inter-menstrual period

Fraenkel (1902), confining his observations to freshly formed corpora lutea as indicated by the red tissue of vascularization, came to the conclusion that ovulation occurs in the second half of the inter-menstrual interval, probably about nine days before the flow appears

Ancel and Villeman placed the date at about twelve days before, while Meyer and Riege placed it thirteen days before, and, from the examination of a certain number of uteri, concluded that the early stage of the Graafian follicle is associated with commencing pre-menstrual changes in the mucosa, that the mature follicle is associated with

the more advanced changes, and that retrogression of the corpus is related to the onset of menstruation

Schroeder placed ovulation fourteen to sixteen days after the onset of the last menstruation, about thirteen days before the next, and found that the corpus may persist into the beginning of the next flow

Sfameni [1] divides the cycle into four phases

1 Rest—Menstrual and postmenstrual, about ten days

2 Activity—Maturation of ovum and rupture of follicle, about five days

3 Rest—three days following

4 Activity—Development of the corpus luteum, about ten days

In confirmation of these results Corner found in the monkey (*Macacus rhesus*) in one animal twelve days before its expected menstruation a ruptured follicle and an ovum in the Fallopian tube, and in another seven days before the period a mature corpus luteum with a fairly degenerate ovum in the uterus

In the pig and other animals, where the connections of the ovum to the uterine muscoa are superficial, the preparation of the mucosa is less marked than in the human subject, while its return to the normal resting condition is more gradual and does not lead to the marked manifestation of menstruation

[1] *Arch Ital de Biol* 1922, 71, 146

The following diagram may serve to show the relationship of the oestrus and the menstrual cycle

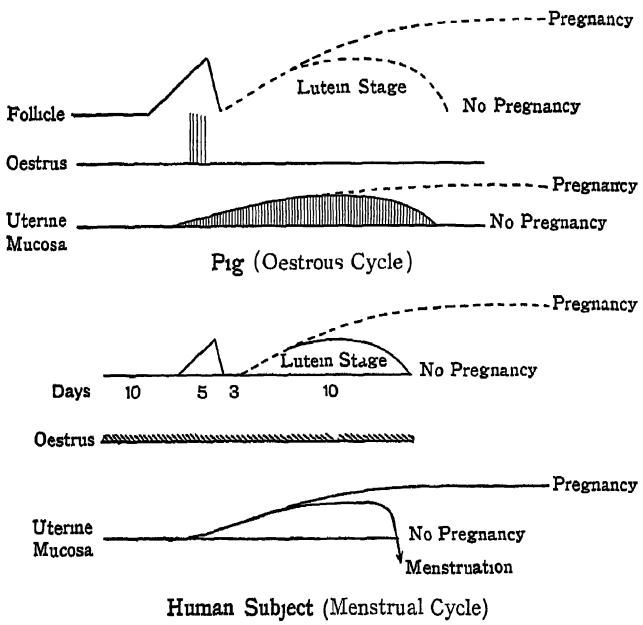


FIG 77.—To illustrate the relationship of the oestrous cycle of the pig with the menstrual cycle in the human subject

These observations go to show that in primates, while ripening of the follicle and ovulation are not connected with oestrus, the formation of a corpus luteum is accompanied by changes in the uterine mucosa preparatory to the embedding of a fertilized ovum Menstruation is then as Corner expresses it "a violent demolition of the pre-menstrual uterine edifice some days after the expected tenant has failed to arrive" It is in fact the end of a brief pseudo-pregnancy

Beard in 1897[1] wrote as follows "Menstruation

[1] *Span of Gestation* Gustav Fischer, p 95

is comparable to an abortion prior to new ovulation, and it is an abortion of a decidua prepared for an egg which was given off subsequently to the preceding menstrual period and which has escaped fertilization"

Somal and Psychic Changes throughout the Menstrual Cycle. It would be surprising if the marked series of changes in the ovaries and uterus which go on during the menstrual cycle were unaccompanied by any alteration in the physiological processes of the body

As is well known a considerable proportion of women feel less well at their menstrual periods, and many suffer from distinct malaise, with headache, fatigue and pain

The figures given by Sturgis [1] and by Sanderson [2] show that the number thus handicapped is comparatively small In an industrial group of 2077 women 65 per cent showed no menstrual handicap, while 30 6 per cent showed only a slight handicap, of 1200 school girls 73 per cent showed no pain or discomfort

Many investigations have been made of the variations in various physiological processes throughout the cycle, but most of them have not been conducted with sufficiently rigid precautions to render them of value

The disturbance in the basal metabolism appears

[1] *J of Indust Hygiene*, 1923, 8, 53
[2] *B M J* 1920 Vol II 511

to be slight, if indeed it actually occurs, and is in the direction of a fall during the period

The temperature shows a premenstrual rise of about a degree Fahrenheit, followed by a fall during the flow

The protein metabolism as indicated by the excretion of nitrogen shows no definite change, but the ammonia coefficient appears to be raised

The circulation shows no marked change except that the pulse is slightly slower and the arterial blood pressure slightly lower during the period The cardio-vascular activity, *i e* the pulse pressure multiplied by the pulse rate, also shows a fall

Muscular strength shows a slight decrease during the period, and a sharp temporary fall on the twenty-third day of the cycle (Moore and Barker) [1]

Muscular and nervous co-ordination, as tested by the selection of balls for bearings at Detroit, was found to be somewhat lowered [2]

The mental activity in perfectly healthy women shows no alteration

Two recent observers, Sieburg and Patschke,[3] record an increase in the cholin in the sweat and in the blood during menstruation, and this has been confirmed by Klaus [4] This may be associated with a greater breaking down of lecithin in the

[1] *Am J of Phys* 1923, 64, 405

[2] Referred to by Taylor, *Principles of Scientific Management*, New York, 1917, p 96

[3] *Ztsch f. ges Exp Med* 1923, 36, 324

[4] *Bioch Ztsch.* 1925, 163, 41

corpus luteum or in the uterine mucosa It is significant that in some cases a characteristic odour from the skin is to be observed

The student may read the Article by Corner in *Physiological Reviews*, 1923, vol. iii, p 457

IMPREGNATION

The endless varieties of adaptation throughout the animal kingdom by which the conjugation of the germ cells is secured cannot here be considered in detail

In some animals vast quantities of these germ cells are liberated into the surrounding water, and their union is secured through the agency of chemiotaxis, the mutual chemical attraction of one cell for the other A similar chemiotaxis in many animals acting through the olfactory organs seems to direct the proximity of the sexes at the time of liberation of the germs Various structural and functional developments may lead to the fixation of the male to the female, as is seen in the seasonal growth of the clasping pads and the development of the clasping reflex in frogs and toads In other animals definite organs of copulation may still better secure this end. In mammals the penis of the male and the vagina of the female are the means by which impregnation is more certainly secured

The **penis** is essentially composed of a mass of distended elastic walled capillaries or sinusoids,

arranged in two cylindrical structures, the corpora cavernosa, which are attached to the ischial and pubic bones, so that when distended with blood the organ is not only greatly enlarged but is also erected The process of erection is primarily brought about by means of a vaso-dilator reflex mechanism in which the receptors are special end structures, the genital bulbs, situated chiefly on the ventral surface of the glans penis, the ingoing nerves are the pudics, and the centre is in the sacral part of the spinal cord The efferent nerves are the pelvic nerves or nervi erigentes, arising from the second and third sacral nerves Stimulation of these leads to dilatation of the arterioles and to an increased flow of blood into the erectile tissue of the penis The increased flow of blood has been shown by placing a canula in the dorsal vein in the penis of the dog, the blood in the vein becomes more arterial Stimulation of the peripheral end of the pudic nerves lead to constriction of the vessels The arteries are spirally distributed so that they may extend in erection, and the lumen is folded, and at places little prominences of the tunica intima act as valves in cutting off the flow of blood when the arteries are constricted When they are dilated these are flattened and do not interfere with the flow

Erection may be brought about as a simple reflex even after section of the cord in the lumbar region But it is more frequently produced as a

conditioned or associated reflex through stimulation of the visual, auditory, tactile, or olfactory mechanisms by stimuli associated with the sexual act Like other spinal reflexes it may be inhibited by the action of the higher brain arcs or by powerful stimuli of various kinds

The erection reflex is activated by the internal secretion of the testes, and it is inadequately produced in the eunuch But when the reflex has once been established castration does not completely abolish it That this action of the internal secretion of the testes is in part at least upon the outgoing nerves or the effector mechanism, *i e* upon the arterioles of the penis, is demonstrated by the observations of Simpson and Marshall[1] that stimulation of the pelvic nerves produces a decreased effect in the dog after castration

In the female the clitoris manifests the same changes as are seen in the penis, but it is directed downwards

Ejaculation of semen is a separate reflex closely associated with the last, but independent of it It is generally brought about by direct stimulation of the genital bodies in the penis by friction against the vaginal wall But it too may sometimes be induced as a conditioned reflex by stimulation of other peripheral sense organs It involves a rhythmic peristaltic contraction of the muscular fibres in the testes, epididymes, vasa deferentia,

[1] *Q J Exp Phys*, 1908, 1, 257

vesiculae seminales and prostate The sperm-containing contents of the tubules of the testes are thus mixed in the urethra with the fluid from the vesiculae seminales, prostate, and Cowper's glands, and driven down to the meatus by rhythmic contractions of the visceral muscles extending from the bladder The striped muscular fibres of the bulbo-cavernous muscle and the ischio-cavernosus also contract rhythmically and expel the semen in jets The orgasm which precedes and accompanies the emission of semen is one of the most extensive reflexes in the body, and its extent is only limited by the amount of the central nervous system involved Thus, in the simple emission which may occur after section of the spinal cord in the lumbar region, only the blood-vessels and muscles of the genital organs are implicated But, when the whole nervous system is intact, the heart is accelerated and its force augmented, the arterial blood pressure rises and the respirations are accelerated The implication of the lower cerebral centres is indicated by the powerful emotional disturbances which accompany copulation

While for successful impregnation a complex reflex mechanism is required in the male, such reflex responses are not required in the female Goltz found that a bitch in which the lumbar region of the cord had been destroyed developed local signs of oestrus, could be impregnated and could produce young

Semen. The semen is a viscous white fluid, opaque on account of the presence of spermatozoa Its reaction is alkaline, and the characteristic odour is due to the prostatic secretion which it contains After excretion it at once becomes gelatinous, but in a few minutes it again becomes fluid Its specific gravity is between 1030 and 1040, and it contains about 10 per cent of solids, among them a mucin-like substance The number of spermatozoa per c mm varies greatly, but the average is about 60,000 The amount of semen emitted at one time varies enormously from less than 1 c c to over 5 c c , and hence the number of spermatozoa in an emission varies Something over 200 million may be considered an average When emissions are frequently repeated, spermatozoa may be absent from the semen The semen consists of spermatozoa from the tubules of the testes along with the secretion of the vasa efferentia, vasa deferentia, vesiculae seminales, Cowper's glands and prostate These secretions activate the spermatozoa, which when taken directly from the testes manifest no movements The rate of progression of the spermatozoa is about 3 to 4 mm a minute, and in the rabbit they have been found on the ovary nine to ten hours after coitus Outside the body they may live for several days, and they are said to have been found living in the female genital passages after three-and-a-half weeks In the bat (p 178) they live in this situation for months

Apparently the secretion of the uterus exercises a positive chemiotaxis upon them

The **prostate** is a dense solid structure about the size of a chestnut, which lies behind the first part of the urethra where the vesiculae seminales open into it It grows as puberty advances and remains of the same size till old age, when it tends to enlarge and when it may press upon and occlude the urethra In eunuchs it remains small throughout adult life It is composed of glands surrounded by strong bands of visceral muscle The secretion of the prostate is a milky fluid, probably slightly alkaline In most animals it activates the spermatozoa and facilitates their movement by diluting the fluid The vesiculae seminales are probably not so much reservoirs of semen as adjuncts to the prostate gland

M'Cartney[1] has discovered that subcutaneous injection of semen into female rabbits produces a condition of infertility Ovulation is not interfered with, but the process of fertilization seems to be prevented Apparently a spermatotoxin is developed

The fact has already been referred to that in some of the hermaphrodite invertebrates the ova are immune to and cannot be fertilized by the sperms of the same individual

[1] *Am J of Phys* 1923, 63, 207

CHAPTER IX

THE NUTRITION OF THE ZYGOTE BEFORE BIRTH (PREGNANCY)

THE matter and energy required for the growth of the embryo may be provided by a storage of proteins, fats and salts in the zygote itself, as is seen in oviparous animals with their large yolk sacs

In viviparous animals, and especially in mammals, it is secured by the connection of the ovum with the lining membrane of the uterus, and by special developments by which the foetal blood is brought into close relationship with the maternal blood

It has generally been assumed that every fertilized ovum is a potential individual, but investigations by Robinson, Corner, and others in ferrets, guinea pigs, and mice show that a considerable proportion of fertilized ova may undergo retrogression and may be absorbed There is no information as to whether or to what extent such early death of the human zygote may occur It is at least probable that it sometimes may escape being embedded and that it may be shed

1 **Embedding of the Ovum.** In the human subject the ovum reaches the uterus in the morula stage measuring about 0 2 mm in diameter From evidence derived from study of the guinea pig it is probable that it remains free in the cavity of the uterus till about ten days after fertilization, when, provided that the uterine mucosa be in a suitable condition, it becomes embedded The corpus luteum plays an important part in this process Fraenkel first showed that removal of the ovaries shortly after impregnation leads to a failure in the fixation of the ovum Taking advantage of the knowledge of the fact that in the rabbit the ovum becomes attached about seven days after it is shed, he removed the ovaries or cauterised the corpora lutea during this period and found that pregnancy was interrupted Removal of the ovaries at a later date did not produce this effect His results have been confirmed by subsequent investigators

The correctness of his conclusion that the corpus luteum produces an internal secretion which acts upon the uterus to prepare it for the fixation of the ovum was further demonstrated by Leo Loeb, who showed that, in the guinea pig, seven days after an unfertilized ovulation which had followed coitus with a male in which the vasa deferentia was ligatured, if a small piece of glass were placed in the uterus the characteristic changes for the reception of the ovum occurred, provided

the corpora lutea were not destroyed These observations have been confirmed and extended by later workers

The embedding of the ovum[1] is brought about by its ectoderm cells growing outward in syncytial processes which form a trophoblast layer and this burrows its way into the sensitized maternal mucosa How this is effected is not known It is assumed that it is due to the development of a powerful proteolytic enzyme, but this has not been demonstrated Certainly in some way the maternal tissues are killed and digested and the maternal blood spaces opened into The blood in them is haemolysed, thus probably rendering the iron of the haemoglobin available for absorption by the ovum.

At this stage of development the embryo is a parasite upon the mother, living upon her substance, and this stage of pregnancy may be called the *parasitic stage* (Fig 78)

The next stage of development may be called the *guest stage*, in which the embryo no longer feeds upon maternal tissues, but shares nourishment with the mother

At the end of about a fortnight, in the human subject, the mesoblast of the embryo extends out in a number of finger-like processes into the trophoblast layer which has formed the primitive villi and soon afterwards blood-vessels shoot into these

[1] Teacher, *J of Obstet and Gynaecol* 1924, 31, 166

and the *chorionic villi* are formed These are at first covered by a definite layer of cubical cells, the layer of Langhans, with outside it a syncytial trophoblast layer of protoplasm Later, the layer

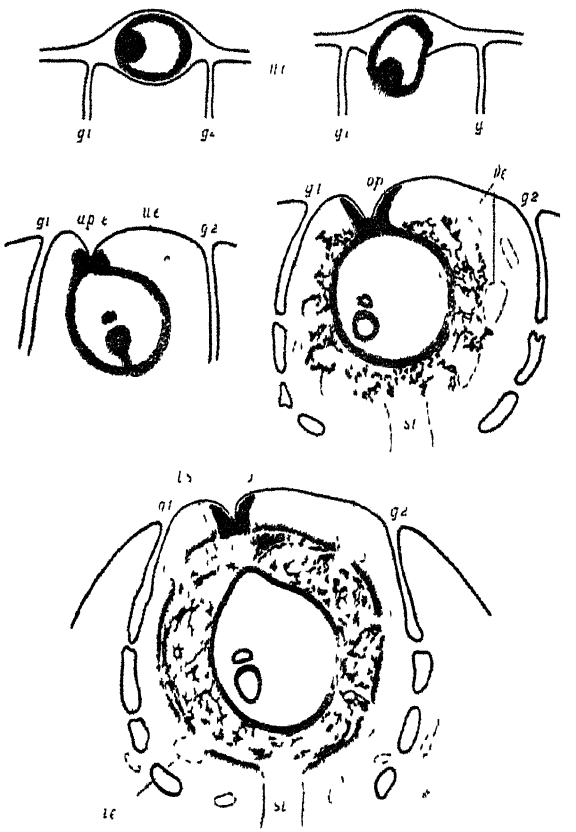


FIG 78—The embedding of the human ovum in the uterine mucosa (Leicher)

of Langhans disappears and the syncytium becomes extremely thin

As development of the ovum advances the blastoderm and the developing embryo sink into the blastocyst, which closes in and forms the *amniotic*

sac This becomes filled with the amniotic fluid, so that the embryo lies in a bath which protects it effectually from external violence

In birds the fluid is certainly formed from the embryo In mammals it has been contended that it is derived from the maternal circulation But, since, as I[1] have shown, in herbivora it resembles urine more than a blood transudate, and since the urethra of the foetus later opens into the amniotic sac, it is probably chiefly derived from the foetal kidneys In rabbits, when the foetus is killed *in utero*, no fluid is formed in the sac, although the maternal part of the placenta persists (B P Watson)[2] A very significant fact is that in herbivora and in other groups of mammals it contains a sugar, laevulose, which is present in the foetal blood but not in the maternal blood

At the end of the pregnancy in the human subject the fluid amounts on an average to about two litres

In the mesoblast, through which the allantoic arteries pass out to the chorionic villi, a vesicle, filled with fluid and at first communicating with the posterior gut, is developed This is the *allantois* In man it never attains any size, but in many of the lower animals it spreads all around and encloses the amnion, and is distended with fluid This fluid has all the characters of urine,

[1] *Phil Trans R S Edin* 1907, 46, 71

[2] *Scot Med and Surg Jour* 1905, 18, No 1

and when fluorescin is injected into the maternal circulation it appears in the foetus before it shows in the allantoic fluid It is almost certainly produced by the foetal kidney

As the foetus develops the allantoic stalk lengthens and finally forms the umbilical cord, a structure averaging about 21 inches in length, through which run the blood-vessels—two arteries and a single vein—to and from the placenta

During the second month of pregnancy the villi over that part of the ovum which lies directly against the wall of the uterus, on the part of the mucosa known as the decidua serotina, form fibrous attachments with the deeper layers of the mucosa while they atrophy over the rest of the ovum This is a critical stage of development, and at this time abortion frequently occurs, while vomiting—"morning sickness"—is generally a prominent symptom in about 50 per cent of pregnancies

2 Placental Stage. The *Placenta* is formed on the foetal side by these processes and on the maternal side by the increased growth and increased vascularity of the decidua serotina of the maternal mucosa.

In the deep layer of the mucosa under the placenta the connective tissue cells enlarge and form a thick mass of clear transparent *decidual cells* Possibly they are protective, preventing the enzymes or other products of foetal metabolism

from invading the mother, certainly they are connected with the accumulation of such nutrient materials as glycogen

The guest stage in the physiological relationship of the foetus to the mother is now fully established The placenta fulfils the functions of (1) the foetal lung, giving the embryo the necessary oxygen and getting rid of the waste carbon dioxide, (2) the foetal alimentary canal supplying the necessary material for growth and development, and (3) the foetal kidney through which the waste nitrogenous constituents are thrown off It is thus the chief organ of the foetus

Independent estimations of the extent of surface of the chorionic villi have been made by Dodds and by Rich, and they agree closely They show a surface of about 6 5 m^2 The surface of the air vesicles of the lungs of an adult measures about 100 m^2, so, taking the weight of the full-time foetus as 3 kilos and that of an adult at 60 kilos, the surface of the villi is greater than the surface of the lungs per unit of weight When the demands of the rapidly growing foetus are considered, the necessity for this large surface of exchange is manifest

Passage of Materials through the Placenta to the Embryo. Carbohydrates are early stored as glycogen in the decidual cells of the maternal placenta, and, since no glycogen is found in the foetus till much later, it must be taken up by the chorionic

villi as sugar (Chipman)[1] Whether the diastase for this conversion is formed by the mother or by the foetus is not known

Fats appear earlier in the foetal chorionic villi than in the maternal placenta (Chipman), and there is no evidence that fats stained with Sudan III are passed to the foetus Probably the foetal fats are formed from carbohydrates

Iron also appears earlier in the foetal part of the placenta than in the maternal (Chipman), and it is probably taken up from the haemolysed maternal blood

As regards the passage of proteins nothing is known with any certainty It may be that the proteins of the maternal blood are passed to the foetus unchanged, but since amino-acids are found in the foetal blood it has been argued that the proteins may be digested to this condition before passing to the foetus It must be recognised, however, that possibly these amino-acids are the results of the protein metabolism of the foetus Chemical examination in ungulates of the allantoic fluid, which is foetal urine (p 199), shows, in the early stage of development, a high proportion of nitrogen in amino-acids, peptides, and allantoin (Lindsay[2]) This seems to indicate a less com-

[1] *Studies from the Royal Victoria Hospital, Montreal*, vol 1 No 4 (Gyn 1), 1902 From work done in the Laboratory of the Royal College of Physicians, Edinburgh

[2] *Biochemical Jour* 1911, 6, 79

plete catabolism of protein and a more active nuclear metabolism than in extra-uterine life.

The placenta manifests little power of regulating the materials which are passed to the foetus, and it allows most drugs and toxic substances to reach it Even the micro-organisms, which are the cause of various diseases, may pass through it This has its advantages, as in all probability immune substances developed in the mother may reach the foetus to afford it protection In this respect it seems to differ from the cells of the choroid plexus which have a selective action on the materials which they pass to the cerebro-spinal fluid and central nervous system

The Demands of the Foetus on the Mother. In the human subject the growth of the foetus is slow, and the daily demands on the mother are small At birth the foetus is less than 8 per cent of the weight of the mother, while in some of the lower animals, *e g* the dog, the litter may weigh 20 or 25 per cent of the maternal weight The following table gives some idea of the rate of growth

WEIGHTS OF FOETUS

1st Month,	- - - -	1 0 Grm
2nd ,	- - - -	2 5 ,,
3rd ,,	- - - -	12 5 ,,
4th ,,	- - - -	90 0 ,,
5th ,,	- - - -	250 0 ,,
6th ,,	- - - -	795 0 ,,
7th ,,	- - - -	1,000 0 ,,
8th ,,	- - - -	1,500 0 ,,
9th ,,	- - - -	2,250 0 ,,
10th ,,	- - - -	3,250 0 ,,

It must be remembered that in the early stages the percentage of solids is much smaller than in the later stages

During its forty weeks of growth the foetus puts on some 550 grm of protein and some 400 grm of fat—less than the amount which the mother would consume in her food in one week without reckoning the carbohydrates of her diet, part of which is available for the formation of fat

Hence, considering the fact that the power of fixing material in the body is increased during pregnancy, the amount of the food consumed which has to be transmitted to the foetus is comparatively trivial

Only in the last two months of intra-uterine life is the demand for proteins, and, more especially, for fats in any way considerable During these months some 120 grm of protein and some 300 grm of fat are added to the foetal body and must be supplied by the mother

It may thus be said that under all conditions of normal nutrition it is the surplus of nourishment which is passed from the mother to the foetus, and, if in the later months of pregnancy her nourishment is limited, the size of the child may possibly be reduced, a possibility which has been taken advantage of to secure the delivery of the child in cases of narrow pelvis Some observations made by me[1] on guinea pigs support the view that the

[1] *Lancet*, 1903, July 4th

weight of the offspring may be thus reduced On this subject further work is required.

The maternal tissues part more readily with some substances than with others Thus, the demands of the foetus for calcium, when the supply of the mother is inadequate, may be met by removal of calcium from her bones, which may be softened and distorted (*osteomalacia*) On the other hand, the maternal tissues do not become depleted of iron in the same way to meet the requirements of the child

As the foetus grows the uterus not only expands but increases enormously in weight This is due to an increase of the muscle fibres in number and in size and to an increase in the elastic fibrous tissue Before pregnancy the uterus weighs about 40 grms—at the end of pregnancy about 1000 grms, a gain of 960 grms, with about 190 grm of proteins

Metabolism in Pregnancy. After the placental circulation is established the maternal body shows the same increased power of storing the constituents of the food as is seen during the period of active growth in children The mother is able to take up what is required to satisfy the normal growth of the foetus, and she frequently retains more than this, thus herself increasing in weight The course of metabolism is not, however, continuous throughout pregnancy Bar has shown that both in the bitch and in the human subject

the body first gains, then loses, then again gains proteins The following table shows this

NITROGEN BALANCE

Bitch	*Human subject*
Gain 15 days	1 to 2 months
Loss 15 days	2 to 4 months
Gain 30 days.	4 to 10 months

Generally throughout pregnancy the increase in the metabolism is proportionate to the increase in the weight of the mother This increase is due not only to the growth of the foetus but also to the growth of the uterus and mammary glands and to the formation of some 2000 grms of amniotic fluid which is inert From this it is manifest that the metabolism of the foetal tissues must be more active than that of the maternal Experiments upon guinea pigs support this conclusion

It has been found by means of the respiratory calorimeter that the total metabolism of the mother just before delivery is practically the same as that of the mother and child after delivery.

CHAPTER X

PARTURITION

In every species of mammal, after a definite period of gestation, the young are expelled in the process of parturition

The stage of development attained varies enormously The marsupial is born in an early condition of development, while the guinea pig at the time of birth is well developed and active and almost independent of the mother Between these all conditions are found The child is born in a somewhat advanced stage of development with the eyes open, and it is capable of very definite movements

Parturition is brought about by the rhythmic contractions of the uterine muscles which have remained quiescent during pregnancy The determining factor is not known It has been suggested that the presence of the corpora lutea may inhibit contraction of the uterus and that their retrogression may allow of its development

Honeyman [1] found evidence of the presence in

[1] Abstracts of Communications, XI[th] Internat Phys Congress, 1923

the serum of parturient women of a substance thermostabile in character which stimulates the isolated intestine and is therefore not adrenalin Dr A Fleming on repeating these observations failed to confirm them Brdiczka[1] states that the serum of parturient women and of women in the ninth and tenth, but not in the sixth or seventh months of pregnancy, and the juice expressed from the placenta induce strong contractions and increased tone in the isolated uterus of the rabbit

The possibility that pituitrin may be the active substance is suggested by Dixon's observations[2] showing that the output of pituitrin is increased by the administration of ovarian extracts, but not by the extracts of the corpus luteum There is, however, no evidence of any hypertrophy of the posterior lobe of the pituitary during pregnancy, although this is so marked in the case of the anterior lobe

Nervous Control. The uterus is supplied by nerves leaving the spinal cord by true sympathetic fibres to the splanchnics These fibres pass to the inferior mesenteric ganglion and proceed in the hypogastric nerves to end in two large plexuses or ganglia, containing numerous nerve cells, one on each side of the cervix, and, from these, fibres pass to the uterus and to the vagina

There is evidence that, in lower animals at least,

[1] *Arch f exp Path Pharmac* 1924, 103, 188

[2] *J of Phys* 1923, 57, 129

the contents of the uterus may be expelled after complete separation of the organ from the central nervous system, the peripheral mechanism, like that of the intestine and bladder, is capable of independent action But normally a centre in the lumbar enlargement of the spinal cord appears to be excited reflexly This centre is further acted upon by the brain, and various disturbances, accompanied by emotional changes, may, for a time, arrest uterine contraction

In the human subject parturition may be divided into three stages In the *first stage* the uterus passes into contractions at intervals, and the lower part or cervix is dilated In the *second stage* the contractions become stronger, and, with the help of the contractions of the abdominal muscles, the child is expelled through the vagina After this the uterus is usually quiescent for a short time, till, in the *third stage*, contractions supervene, and the placenta and membranes lining the uterus are expelled as the *after-birth*

CHAPTER XI

NUTRITION OF YOUNG AFTER BIRTH

LACTATION

In oviparous animals, *e g* in fish and birds, a greater and lesser residue of the yolk remains attached to the young to furnish nourishment during the earliest period of independent life

In mammals the mammary gland supplies the required nutrient as milk

The mammary gland may be considered as one of the secondary sexual structures It is fundamentally a special development of the sebaceous system of cutaneous glands, but in marsupials it is said to resemble sweat glands in structure In these animals there are no nipples, but the glands open in pores

In considering the physiology of the mammary gland a distinction must be made between its growth and its functional activity

Growth. In its early stage of development it consists of a few branching columns of cells radiating from a central point, the nipple It is found in foetal life in both sexes, and immedi-

ately after birth it may reach such a stage of development that it secretes milk (witches' milk)

Early ovariotomy prevents the small growth of the mammary gland which occurs in young animals, and which in the human subject is so markedly accelerated with the onset of ovulation and puberty Hence the ovaries must be an important factor in determining this growth, and, since the increase occurs so rapidly at puberty, it would seem that some product of the ripened Graafian follicles or of the corpora lutea must be the active agent in inducing this

Steinach has shown that the transplantation of ovaries into castrated male guinea pigs leads to growth of the gland and to secretion of milk Curiously enough Lipschutz finds that this hyper-development does not occur when additional ovaries are transplanted into females

Knott (quoted by Marshall) cites cases of men, a bull, a male goat and a wether, which secreted milk and suckled Such cases are rare, and in the light of our knowledge of hermaphroditism, the possible influence of the presence of ovarian tissue cannot be ignored

The relationship of the ovary to the gland is confirmed by the enormous increase which occurs during pregnancy, when the large corpus luteum or corpora lutea of pregnancy are formed

The correlation of the gland with the ovaries may be represented in Fig. 79.

The possibility of inducing a pseudo-pregnancy has facilitated the study of the factors determining growth of the mamma By cutting the vasa deferentia in male rabbits and allowing coitus ovulation is secured without impregnation The same end may be secured by ligaturing the Fallopian tube of the female It is found that the

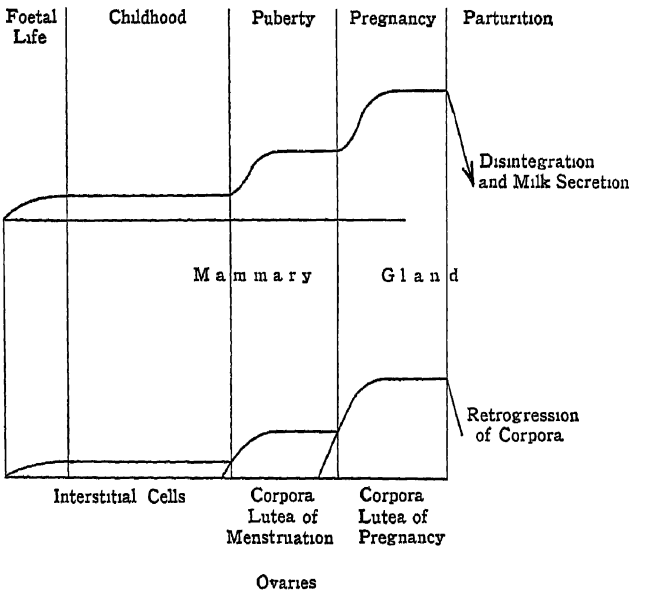


FIG 79 —To illustrate the changes in the mammary gland to the condition of the ovaries

corpora lutea, after such a coitus, persist for a considerable time, that the changes of early pregnancy go on in the uterus (p 196), and that the mammary gland enlarges and may secrete

Leo Loeb (quoted by Marshall) states that removal of the corpora lutea prevents the active proliferation of the gland which occurs in the

later stages of pregnancy On the other hand, ovariotomy late in pregnancy does not prevent milk secretion, which is the culmination of the growth of the gland

That an internal secretion from the placenta does not play an essential part in determining the growth of the gland seems to be indicated by Hammond's experiment, in which he produced the formation of decidual tissue in the uterus of the rabbit by Loeb's method (p 181) and found no further development of the mamma than that which occurs when this formation had not been induced He found, moreover, that if in pregnancy the foetus be removed and the placenta left no secondary growth changes occur in the gland

This last observation seems to point to the possibility of some internal secretion from the foetus playing a part in the growth of the gland in pregnancy But since the gland grows in pseudo-pregnancy without the presence of foetuses this cannot be a prime factor Lane Claypon and Starling found that repeated injections of extracts of foetal rabbits into virgin rabbits causes a marked growth of the gland, culminating in secretion of milk Boiling the extract did not destroy its activity But manifestly an internal secretion from the foetus has nothing to do with the normal growth of the gland in the virgin Apparently the presence of the foetus acts upon the corpus luteum to increase and to prolong its

growth, and it may in this way secondarily influence the mammae

There seems little evidence in support of the theory advanced by Bouin and Ancel that cells in the uterus produce an internal secretion acting upon the mammae Their observation on the presence of a myometral gland has not been confirmed

Secretion of Milk. The production of milk consists first in the breaking down of cells in the acini of the gland and the formation of *colostrum*, and second in the secretion of true *milk*

While the cells in the centre of the acini are breaking down those upon the basement membrane begin the production of milk Thus the fluid which first escapes from the gland—the *colostrum*—is really milk plus the desquamated cells with the products of their disintegration and emigrated leucocytes

Under the microscope it shows cells, the colostrum corpuscles, in the process of breaking down, and in addition to the usual milk constituent it contains albumin and globulin, and therefore coagulates on boiling. It is richer in inorganic salts than true milk

If the growth of the gland be determined by the presence of the corpora lutea, the retrogressive change should be correlated with the decrease in the corpora The course of pseudo-pregnancy in the rabbit shows this to be the case. Further, it

has been found that in bitches, after oestrus, the mammary gland frequently grows and finally secretes, so that the animal may suckle pups Hammond has shown that here too there is a persistence of the corpora lutea But, just as the growth of the corpora is less marked and less prolonged than when pregnancy supervenes, so the growth of the mamma is less marked and reaches its maximum sooner

The evidence thus indicates that the growth of the gland in pregnancy is controlled by a product of the corpora lutea and that the retrogressive changes which precede true secretion may be determined by the withdrawal of this product

Castration of a cow in milk prolongs lactation over a period of years, but in some animals, *e g* the rat, the corpora lutea persist into lactation Unfortunately from its structure it is not generally possible to deduce the functional activity of a ductless gland, and it may be that the production of its special internal secretion may have stopped without any visible change

Lactation may be induced even in the virgin animal by stimulation of the nipples This has been observed in heifers, mares and in girls That stimulation of the nipple acts upon other organs is well shown by its influence upon uterine contractions Its action can be explained only as a reflex acting either directly upon the gland tissue through the nerves or indirectly by calling

forth some internal secretion which acts upon the gland The evidence that the gland acts apart from the nervous system is very conclusive Ribbert grafted mammary tissue near the ear in a guinea pig and found that during pregnancy it enlarged and secreted milk

But that the nervous system does act directly or indirectly upon the gland is demonstrated by the influence of nervous disturbances upon the quantity and quality of milk in nursing mothers The mode of action of stimulation of the nipples must be left an open question

Milk. When true milk secretion is established, the epithelial lining of the acini is reduced to a single layer of cells which separate from the plasma or elaborate from precursors in the plasma the constituents of milk

The milk of all animals contains characteristic proteins, sugars and fats, with certain inorganic substances

The protein, *caseinogen*, is a phospho-protein linked to calcium, but, in addition, traces of native proteins may be present

The sugar is the disaccharid *lactose*, which splits into dextrose and galactose

The fats exist in fine globules of varying size and consist chiefly of olein, with some of the fats of the lower fatty acids, *e g* butyric acid

Milk is specially rich in calcium and in phosphoric acid in organic and inorganic combinations

The mammary gland undoubtedly synthesizes the caseinogen, which contains all the amino-acids required by the body except glycin which is readily formed from the others

The gland appears to use the glucose of the blood for the production of lactose, but the source of the galactose with which it is combined is entirely unknown The fats of the milk differ from those of the plasma, and are also probably synthesized in the gland

The inorganic constituents are generally in higher concentration than they are to the plasma, and their proportion corresponds closely with that in the body of the suckling young

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